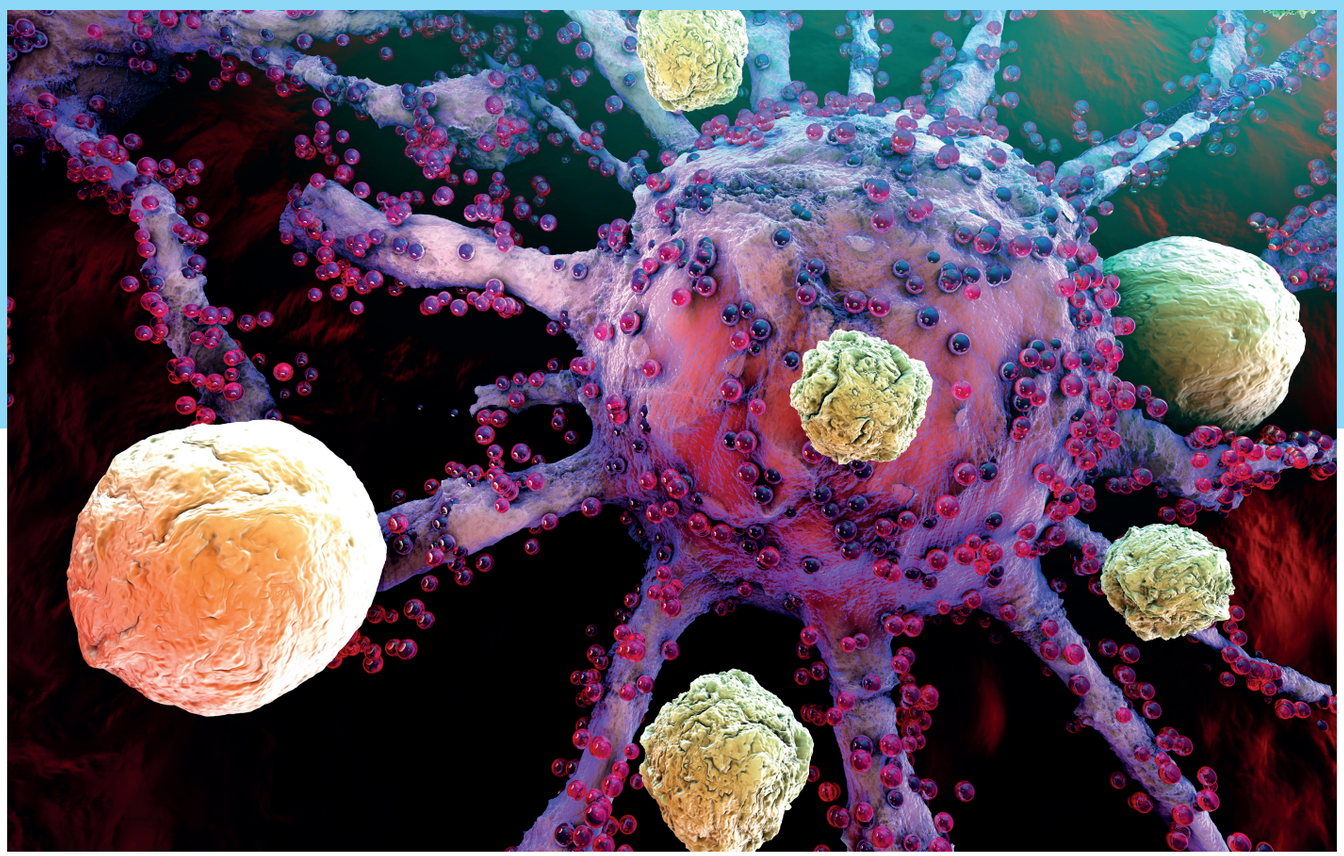
ISSN 0971-5851
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

Number 1 • Volume 46 • Pages 1–118 • February 2025



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ISSN 0971-5851
eISSN 0975-2129

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Indian Journal of Medical and Paediatric Oncology is published 6 times a year in February, April, June, August, October, and December by Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India. Tel: +91-120-4556600, Fax: +91-120-455-6649.

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Typesetting: Thomson Digital, Noida, India
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Volume 46, Number 1/2025

Indian Journal of Medical and Paediatric Oncology

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ISMPO Guidelines for Diagnosis and Management of Early Breast Cancer

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Ind J Med Paediatr Oncol 2025;46:1–23.

Abstract

The management of breast cancer has become increasingly complex and multidisciplinary in the recent past. Further, there are unique constraints and opportunities for cancer care delivery in India, including socioeconomic, geographic, and other disparities. Therefore, the Indian Society of Medical and Paediatric Oncology convened a panel of experts to create evidence and context-based guidelines for the management of early breast cancer.

Keywords
- early breast cancer
- guidelines
- ISMPO
- medical oncology

Introduction

The incidence of breast cancer has been gradually increasing in India in the past few decades and it overtook cervical cancer as the most common cancer among women in 2020.[1] Based on data from population-based cancer registries, the age-adjusted annual incidence of breast cancer in large urban locations in India is approximately 30 to 35/100,000, with an average annual percentage increase of about 1.1%, and in rural locations about 10 to 12/100,000.[2,3]

The most important risk factors for breast cancer are increasing age, genetic predisposition,[4] obesity, lower parity,

article published online
July 18, 2024

DOI https://doi.org/10.1055/s-0044-1786517.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

and exposure to estrogen, including use of hormone replacement therapy. Apart from the known high-penetrance germline mutations in a few genes like *BRCA* 1 and 2, research has evaluated that, in the Indian population, the association of body fat distribution (increased waist–hip ratio) is associated with breast cancer risk.[5,6] There is some evidence that physical activity,[7] dietary modification,[7] and adequate breastfeeding[8] can be protective.

India is a large country with varied geography, different disease distribution pattern among rural/urban society, and socioeconomic constraints which make management of early breast cancer complex and different. Therefore, the Indian Society of Medical and Paediatric Oncology convened a panel of experts to create evidence and context-based guidelines for the management of early breast cancer. Various key opinion leaders from pathology, radiology, molecular oncology, medical, radiation, and surgical oncology have thoroughly discussed and put down the recommendations (Strength, Grade) applicable to our country.

Diagnosis of Early-stage Breast Cancer

Mammography is the gold standard worldwide for screening and diagnosis with the maximum benefit in some studies shown to be between 50 and 60 years. However, India has a high incidence (up to 33% of all incident breast cancers in some studies) of cancer in younger females.[9,10] There are currently no established screening standards that advocate for the routine screening of women under the age of 40 who are at average risk. In the population of women under the age of 40, the occurrence of breast cancer is relatively infrequent and young women have dense breast, hence the mammogram can be misleading and lead to false negatives. Additionally, there is a lack of randomized studies pertaining to breast cancer screening, and the efficacy of mammography in this context is suboptimal. For younger females, clinical and self-breast examination along with ultrasound (USG) breast can be adjuncts to mammography but cannot replace mammography. The implementation of biennial clinical breast examinations by primary health care providers resulted in a notable decrease in the stage of breast cancer at the time of diagnosis. Additionally, this intervention was associated with a reduction in breast cancer mortality, although the overall reduction was not statistically significant. However, a substantial reduction of almost 30% in mortality was observed specifically among women aged 50 years and older. The inclusion of clinical breast examination as a component of breast cancer screening should be given due consideration in our country.[11]

In patients at high risk of developing breast cancer (estimated lifetime risk of >20% such as—women with personal history of breast cancer, *BRCA 1* and *2* gene mutation carriers or their first-degree relatives, women with a history of chest irradiation between 10 and 30 years of age, Li–Fraumeni syndrome [P53], or above syndromes in first-degree relatives); current evidence-based screening guidelines (►**Table 1**) include earlier and more frequent screening, with the addition of annual breast MRI.[12,13]

Early-stage breast cancer would include tumors which are palpable (T1b, T1c, and T2) with or without palpable axillary lymphadenopathy (N1). With palpable masses, there is a need for a diagnostic imaging workup as per the below guidelines (►**Table 2**). Indication of MRI during early breast cancer diagnosis is detailed in ►**Table 3**.

Pathology

Pathological diagnosis of breast cancer is amalgamation of histomorphology, biomarker assessment, and multigene assays. Core needle biopsy is a highly sensitive and specific modality with excellent diagnostic agreement and is mandatory prior to commencement of any treatment. It is a modality of choice for obtaining tissue diagnosis from primary breast lesion and axillary lymph node if metastasis is suspected. ►**Table 4** enumerates the basic investigations required at the time of diagnosis.

Optimal tissue handling should be ensured with minimal cold ischemia time to enable adequate fixation for histopathology and immunohistochemistry (IHC) assays. The pathology report should be generated in a standard format outlining clinically relevant factors and prognostic information. Tumor size, histological grading (Nottingham combined histologic grade), peritumoral/lymphovascular invasion, in situ component, and tumor infiltrating lymphocytes are other parameters of importance to be outlined in pathologic report.

The pathologic staging should be carried out in accordance with Union of International Cancer Control and American Joint Committee for Cancer (Eighth Edition) for Tumor, Node, and Metastasis staging system.[14] In current staging system, pure anatomic staging is integrated with prognostic modifiers—histologic grade, estrogen receptor (ER), progesterone receptor

Table 1 Screening recommendations

	LoE	GoR
• It is advised that women between the ages of 50 and 69 get mammography screening.	I	A
• Regular mammography screenings may also be conducted for women between the ages of 40 and 49, as well as those between the ages of 70 and 74. However, it should be noted that the data supporting the benefits of mammography in these age groups are not as well established.	II	B
• In women with a strong familial history of breast cancer, with or without proven BRCA mutations, annual MRI and annual mammography (concomitant or alternating) are recommended.	I	A

Abbreviations: GoR, garde of recommendation; LoE, level of evidence.

Table 2 Imaging recommendations

Age group (years)	Imaging modality	LoE	GoR
<29	Ultrasound (USG) modality of choice	I	A
30–39	USG	I	A
>40	Both mammography and USG to be performed with mammography as the initial modality	I	A

Table 3 Recommendations for role of magnetic resonance imaging in early breast cancer

	LoE	GoR
Familial breast cancer associated with BRCA mutations	I	A
Lobular cancers	I	A
Dense breasts	II	B
Suspicion of multifocality/multicentricity (particularly in lobular breast cancer)	I	A
Large discrepancies between conventional imaging and clinical examination	III	B
When the findings of conventional imaging are inconclusive (such as a positive axillary lymph node status with an occult primary tumor in the breast)	I	A

Table 4 Recommendations for pathology

	LoE	GoR
If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers	I	A
As a minimum, USG fine-needle aspiration or core biopsy of suspicious lymph nodes should be carried out, preferably followed by clip or carbon marking of biopsied lymph nodes	III	A
Pathological evaluation includes histology from the primary tumor and cytology/histology of the axillary nodes (if involvement is suspected)	I	A
Pathological report should include histological type, grade, IHC evaluation of ER, PgR (for invasive cancer), HER2 (for invasive cancer)	I	A
[a]Ki-67 proliferative index below 5% or above 30% could be used as prognostic marker	IV	B
Tumors should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data	I	A

Abbreviations: ER, estrogen receptor; IHC, immunohistochemistry; USG, ultrasound.
[a]Recommended cutoff for Ki67 high/low—20%[17].

(PR), human epidermal growth factor receptor 2 (HER 2) expression, and Ki proliferation index. American Society of Clinical Oncology—College of American Pathologists guidelines strongly recommend ER and PR testing of newly diagnosed invasive cancer by validated IHC. The results should be expressed in standard scoring system (Allred or H score). Nuclear staining between 10 and 100% is considered positive and between 1 and 10% should be reported as low positive. The low-positive reporting category with 1 to 10% expression *does not* apply to PR. The results should express overall positivity and not hotspots as the staining may be heterogeneous.[15] HER 2 expression can be evaluated by IHC and *HER2* gene amplification by in situ hybridization (ISH), which could be fluorescent, chromogenic, or silver-enhanced. Score of 2+ is considered equivocal and followed by reflex *HER2* gene amplification by ISH either by dual probes (preferred) or single probe studies. Ki67 proliferative index is of clinical utility in prognostication and potential chemotherapy benefit but is limited due to lack of international consensus on scoring methods, cutoff values, and reproducibility. International Ki67 breast cancer working group agreed that Ki-67 proliferative index below 5% or above 30% could be used as prognostic marker.[16]

Breast carcinomas should be categorized into surrogate intrinsic subtypes for prognostication and therapeutic decisions (►**Fig. 1**). For prognostic risk stratification and prediction of chemotherapy benefit, molecular profiling of early-stage ER positive, HER-2 negative breast carcinomas is advised.

Predictive and Prognostic Multigene Assays in Hormone Receptor-positive/HER2-negative Early Breast Cancer

In patients with early-stage breast cancer, the decision of systemic adjuvant therapy is often based on the clinicopathological factors defining the risk of relapse, response prediction to specific treatment (endocrine vs. targeted), its

Intrinsic subtype	Surrogate subtype	IHC	Grade	Outcome
Luminal A	Luminal A like	ER positive PR positive HER 2 negative Ki67 proliferative index: low*	1/2	Good
Luminal B	Luminal B like Her2 negative	ER positive HER 2 negative Any one of the following • Ki67 high* or • PR negative	2/3	Intermediate
	Luminal B like Her2 positive	ER positive HER 2 positive PR : any Ki67 proliferative index: any	2/3	Poor
HER 2 postive (non-luminal)	HER 2 overexpression	ER negative PR negative HER 2 positive	2/3	Poor
Basal	Triple negative	ER negative PR negative HER 2 negative	3	Poor

* Recommended cut off for Ki67 high/low – 20% [17]

Fig. 1 Breast molecular and surrogate subtypes. Er, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor.

benefits and toxicities. The risk of relapse particularly in HR-positive, HER2-negative tumors is assessed by age, menopause status, number of positive nodes, primary T stage, grade, Ki67, and multigene assays.

Predictive and Prognostic Assays

Among various commercially available multigene-based assays, Oncotype DX is supported by clinical validation not only for estimating prognosis but also for predicting the recurrence risk reduction when chemotherapy is added to hormone therapy (►**Fig. 2a**). Patients with more than 1.0 cm, node negative, hormone positive with recurrence score of 0 to 10, does not warrant adjuvant chemotherapy, only endocrine therapy (ET), as compared to high recurrence score (RS) (>25) which will demonstrate a clear benefit on adjuvant chemotherapy.[18,19] Based on the TAILORx trial, RS 11 to 25 (intermediate risk) did not show any additional benefits of adjuvant chemotherapy over and above ET. However, for women aged less than 50 years, RS score from 16 to 25, did reveal lower risk of recurrence (ROR) when chemotherapy is added to postoperative hormone therapy.[19] As per Rx PONDER study, postmenopausal women with recurrence risk <26, node positive (1–4 nodes) did not show any benefit of adjuvant chemotherapy. On the contrary, N1, young premenopausal females in the same study revealed benefit of adjuvant chemotherapy in addition to adjuvant ET in node-positive patients irrespective of RS.

Prognostic Assays

70-gene assay (MammaPrint) can classify the patients into genomic low or high risk for distant recurrence. However, based on the randomized MINDACT published data, the utility of 70-gene signature in providing evidence for making recommendations regarding the use of adjuvant chemotherapy especially for patients at low clinical risk[20] is not present, thus having only prognostic significance (►**Fig. 2b**).

50-gene assay (PAM50) has only prognostic clinical value *and* can identify the ROR and stratify patient into high-, medium-, and low-risk groups. Based on Danish Breast Cancer Cooperative Group database and TransATAC study, low ROR with either lymph node-negative or -positive tumors, had low risk for distant recurrence.[21,22]

12-gene assay (EndoPredict) calculates the risk score and stratify the patients into low and high risk of distant recurrence. Patients with an RNA-based 12-gene low-risk score, predicts late recurrences risk among low-risk patients (less than 2 cm and more than 2 cm but node negative). TransATAC study, retrospectively validated endo predict (EP) and EP clin

a

Oncotype DX assay	Recurrence risk	Treatment implications
21-gene Oncotype DX Postmenopausal patients with pN0 and pN1 (1–3 positive nodes)	<26	No benefit from the addition of chemotherapy to endocrine therapy
	≥26	Addition of chemotherapy to endocrine therapy is recommended
21-gene Oncotype DX Premenopausal patients with pN0	≤15	No benefit from the addition of chemotherapy to endocrine therapy
	16–25	Small benefit from the addition of chemotherapy exists. Consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI
	≥26	Addition of chemotherapy to endocrine therapy is recommended
21-gene Oncotype DX Premenopausal patients with pN1	<26	Benefit from the addition of chemotherapy exists. Consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI
	≥26	Addition of chemotherapy to endocrine therapy is recommended

b

MammaPrint		
Clinical risk	Genomic risk	
	LOW	HIGH
LOW	Endocrine therapy	Uncertain chemo benefit
HIGH	Chemo (discuss OFS and AI as an alternative)	Chemo
	Clinical risk high if expected 10 years OS <92% with ET as per adjuvant online	

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; OFS, ovarian function suppression; OS, overall survival.

Fig. 2 (a) Oncotype DX-based risk stratification. (b) MammaPrint-based risk stratification.

Table 5 Assay

	LoE	GoR
21-gene (Oncotype DX; for pN0)	I	A
21-gene (Oncotype DX) for pN1 (1–3 positive nodes)	II	A
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	I	A
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	II	B
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	II	B
Breast Cancer Index	II	B
CanAssist Breast	IV	C

scores in patient with low risk of of distant recurrence,[22] suggest that adjuvant chemotherapy may not yield additional benefit in these patients.

Breast Cancer Index (BCI) is an RT PCR-based assay that combines gene expression of two biomarkers the HOXB13: IL17BR ratio (H/I), and Molecular Grade Index (MGI).[23] It helps us to predict risk of late distant recurrence (5 years postdiagnosis) and also cumulative risk of relapse at 10 years in female treated only with adjuvant ET for node-negative and chemo-ET in N1 patients.

Patients with a BCI low-risk score, the T1 and T2, and lymph node-negative tumors prognostic category is similar to T1a–T1b, N0, M0. BCI has only prognostic clinical value.

CanAssist Breast is an IHC-based test developed and validated on more than 2,000 patients primarily of Indian ethnic origin. It calculates the risk score and stratifies the patients into low and high risk of distant recurrence. This test assesses the expression of five biomarkers (CD44, ABCC4, ABCC11, N-Cadherin, pan-Cadherin) involved in tumor biology, namely metastasis, drug resistance, stemness, and arrives at a score predictive of distant recurrence, along with three clinical parameters—tumor size, grade, and node status.[24] The same has not been validated in any prospective randomized control trial. ►**Table 5** mentions recommendations for various genomic prognostic assay available to us for deciding adjuvant therapy for both node-negative and -positive (<4) early breast cancer.

►**Fig. 3** depicts the algorithm to be followed for the interpretation and applicability of the current RS cutoff score in Oncotype DX assay results.

Management

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) was a relatively rare entity till the advent of routine screening programs. DCIS now constitutes about 20 to 25% of "Stage 0" breast cancer. National Cancer Institute study of 2020 reported a 36 to 100% progression of DCIS to invasive cancer when not treated. The progression time was 0.2 to 2.5 years; however the overdiagnosis of DCIS was 3.1 to 65.8%.[25]

DCIS needs a multidisciplinary team approach. Mastectomy or breast conservation surgery (BCS) along with radiation are the cornerstones of management. Total mastectomy with clear margins along with reconstruction in DCIS is curative, and radiation therapy (RT) is usually not recommended. There is no general agreement on what is considered an optimal margin; however, recent consensus has determined that a 2-mm margin is adequate.[26] ►**Table 6** mentions the indication of adjuvant radiotherapy and/or hormone therapy, postsurgery for DCIS. RT is commonly used as the standard treatment for patients undergoing breast-conserving therapy (BCT). However, it may be justifiable to exclude certain individuals with advanced age, significant comorbidities, or small areas of low-grade disease that have been surgically removed with wide negative margins.

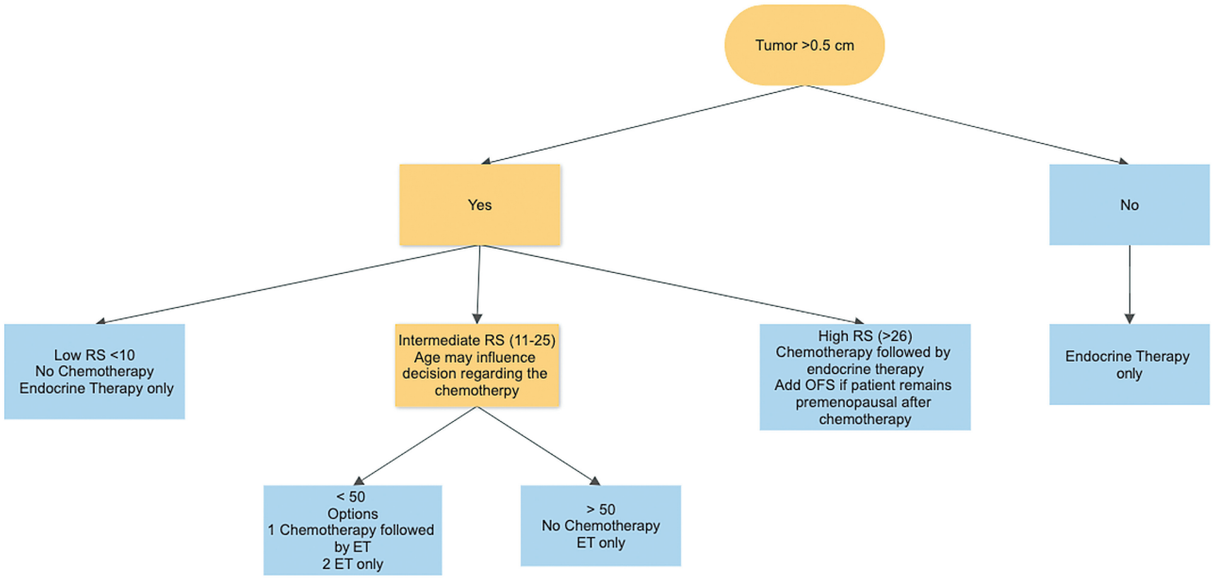

Fig. 3 Algorithm for adjuvant therapy for HR + EBC > 0.5 cm. ET, endocrine therapy; OFS, ovarian function suppression.

Table 6 Recommendations for ductal carcinoma in situ

	LoE	GoR
BCS followed by whole breast radiotherapy or total mastectomy is acceptable treatment options for DCIS	I	A
Whole breast radiotherapy is recommended for the majority of women with DCIS treated with BCS	I	A
In patients with low-risk DCIS, omitting radiation is an option	V	B
Both tamoxifen and Ais may be used after conservative, local treatment of DCIS to prevent local recurrence and to decrease the risk of development of a second primary breast cancer	I	B

Abbreviations: AI, BCS, breast conservation surgery; DCIS, ductal carcinoma in situ.

ET in the form of tamoxifen or aromatase inhibitors (AIs) used in ER and PR positive disease reduces the risk of local recurrence as well as of contralateral breast cancer. Tamoxifen is not commonly used as a chemopreventive measure for women diagnosed with ER − DCIS due to the lack of evidence supporting its efficacy in reducing the risk of disease recurrence in this specific subgroup. Certain individuals of the female gender may choose to utilize tamoxifen as a means to mitigate the likelihood of acquiring a fresh case of ER + DCIS or breast cancer. In women having bilateral mastectomies for DCIS, the risks of adverse effects from tamoxifen outweigh any potential benefit for risk reduction.

Targeted therapy for HER2-positive disease is controversial with the NSABP B-43 data showing some benefit but we do not recommend the use of trastuzumab.[27]

Surgical Management of Early Breast Cancer

Management of Palpable Primary (T1/T2)

In early breast cancer, the choice between BCS followed by RT or mastectomy usually depends on size and location of tumor, tumor to breast size, multicentricity, lymph node involvement, and patient factors such as age, menopausal status, and personal preferences.

Safety of BCT-NSABP-06 trial found no significant differences among women who underwent lumpectomy followed by radiation or mastectomy with respect to disease-free survival (DFS), distant diseases free survival (DDFS), or overall survival (OS).[28] In a study in the Netherlands of 37,207 patients who underwent BCT found significantly improved 10-year OS compared with mastectomy in all T and N stages of breast cancer. Clear or negative margins are mandatory for optimal outcomes of BCT. "No ink on tumor" is the standard margin for breast cancer patients treated with BCT.[29] Positive margins have been associated with a two-fold increase in local recurrence rate. Neither radiotherapy nor systemic therapy can substitute for re-excision to clear margins.

►**Tables 7** and **8** show the recommendation for management of primary and axilla, respectively, in patients who have not undergone chemotherapy.

Management of Primary Postneoadjuvant Chemotherapy

All patients must undergo definitive breast surgery, after the completion of neoadjuvant therapy, even with complete response. Metal clips should be placed in tumor bed under ultrasound guidance in all patients considering BCT before neoadjuvant treatment is started. Imaging should be repeated postneoadjuvant therapy to assess tumor response and for surgical planning. Feasibility of BCS is dependent on posttreatment tumor size and characteristics and not pretreatment tumor size. Following neoadjuvant treatment, the imaging modality that most clearly showed the extent of the disease upon presentation is probably the most informative. On the other hand, the choice of imaging modality and whether to acquire posttreatment investigations may be determined by factors related to surgical planning (►**Table 9**).

Table 7 Management of primary

	LoE	GoR
BCS is the preferred treatment option for locoregional treatment of EBC	I	A
No tumor at inked margin is required to minimize local recurrence	I	A
Mastectomy may be offered for multicentricity, BRCA-positive individuals, and for cosmetic reasons. We recommend immediate reconstruction postmastectomy.	V	A

Abbreviation: BCS, breast conservation surgery.

Table 8 Management of axilla

	LoE	GoR
SLNB is standard of care for clinically and histologically negative axilla	I	A
Complete ALND can be avoided in SLNB negative or one to two SLNB-positive patients	II	A

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Table 9 Management of EBC postsystemic therapy

	LoE	GoR
All patients must undergo definitive breast surgery BCT/mastectomy, after the completion of neoadjuvant therapy, taking into consideration the tumor characteristics and response posttherapy.	II	A
SLNB is recommended in patients with node-negative axilla prior to systemic therapy	II	A
SLNB may be performed in selected cases in patients with node-positive axilla converting to node-negative postsystemic therapy	II	B
Completion ALND is recommended in patients with SLNB-positive patients postsystemic therapy	II	B

Abbreviations: ALND, axillary lymph node dissection; BCT, breast-conserving therapy; SLNB, sentinel lymph node biopsy.

Mastectomy and Oncoplasty in Special Situations

Mastectomy in early breast cancer is usually performed as per patient choice or tumor characteristics (inflammatory breast cancer/diffuse microcalcifications/multicentric/inability to attain negative margins/pregnancy/contraindication to RT) making it nonfeasible for BCT. Oncoplasty is ideally suited for patients who have a large tumor relative to their breast size, or preexisting aesthetic concerns as it permits removal of large volume of tissue while preserving natural appearance. Oncologic outcomes of oncoplastic surgery are comparable or superior to those of standard BCT with low reported complication rates.[30] All patients should be offered immediate breast reconstruction (with the exception of inflammatory breast cancer). Breast reconstruction procedures can be performed either immediately following a mastectomy or in subsequent surgical intervention. Immediate reconstruction is a viable option for the majority of individuals who are undergoing mastectomy. This encompasses patients who undergo preventative mastectomy as well as mastectomy for invasive or in situ cancer. The consideration of delayed reconstruction is warranted in patients diagnosed with inflammatory breast cancer, as well as in patients who have a higher likelihood of experiencing negative results due to comorbidities. Additionally, the preferences of both the patient and the surgeon should be taken into account while making this decision. Staged-immediate reconstruction is occasionally considered in patients with inadequate perfusion of the mastectomy skin flaps as a technique of minimizing the likelihood of delayed healing and reconstructive failure. Patients belonging to this particular type typically exhibit the capacity to recommence the process of reconstruction within a span of 2 to 4 weeks, subsequent to the attainment of complete recovery. There was no observed increase in problems associated with postmastectomy RT, regardless of whether the reconstruction procedure was performed immediately or delayed.

Multicentric Lesions

Multicentric disease with two or more primary tumors in separate quadrants of the breast such that they cannot be encompassed in a single excision is considered an absolute contraindication to BCT. The Alliance Z11102 trial, 198 women with two (96%) or three (4%) separate sites of biopsy-proven malignancy separated by $\geq$2 cm within the same breast underwent BCS. BCS was feasible in 93% and achieved with a single operation in 73%, only 7% required mastectomy due to positive margins. At 2 years, the majority of women who underwent BCT reported good-to-excellent cosmesis.[31] However, long-term recurrence data are required before any recommendation can be made to permit use of BCS in multicentric disease.

Risk-reducing Mastectomy

Hereditary breast cancer patients (e.g., -BRCA carrier) should be informed about their increased risk of a second primary cancer from 2 to 5% per year and that bilateral mastectomy may reduce the risk of a second primary. However, contralateral prophylactic mastectomy in such patients only decreases incidence of metastatic contralateral breast cancer without any improvement in OS.[32] High-risk patients are not barred to BCT, but the decision should be made following extensive discussion with an experienced surgeon and a genetics counsellor.

Skin-sparing Mastectomy

This is preferred only for breast cancer patients with low rates of local recurrence due to early stage, biologically favorable cancers, and/or DCIS that are located >2 cm from nipple. Retrospective studies indicate that skin-sparing mastectomy does not increase risk of local recurrence while offering the advantage of natural skin cover and immediate reconstruction.[33]

Management of Nonpalpable Primary

Lumpectomy in nonpalpable lesions is performed with the use of localization techniques J wire/radioactive seed localization (RSL)/radio occult lesion localization (ROLL) and excision followed by confirmation with specimen mammogram. No difference in margin positivity rates between ROLL and needle localization or RSL has been observed.[34]

Management of Axilla

A thorough axillary evaluation consisting of clinical examination, axillary imaging, fine needle aspiration cytology (FNAC)/biopsy of suspicious lymph nodes, and clipping before neoadjuvant therapy is required.

Axilla Sampling in Indian Setting

Limited axillary dissection via sentinel lymph node biopsy (SLNB) is standard of care in node-negative operable breast cancer. However, the high cost of the gamma probe and the need for radiocolloid have limited its widespread acceptance

in developing countries. Low axillary sampling (LAS) is a safe alternative to SLNB in countries with limited resources due to similar false negative rates. Therefore, LAS is an effective and low-cost procedure that minimizes axillary surgery and can be implemented widely.[35]

LAS can also be used to de-escalate axillary surgery in postchemotherapy patients, as it is superior to SNB in identification rate, FNR, and negative predictive value in predicting node-negative axilla postneoadjuvant chemotherapy (NACT). LAS can be safely used to predict negative axilla with <10% chance of leaving residual disease.[36]

Management of Clinically Negative Axilla

SLNB is the standard initial approach for women with clinically node-negative early breast cancer (EBC).[37] Patients with negative pathology results from fine needle aspirate or core biopsy of image detected abnormal lymph nodes should also be considered for SLNB. We recommend to omit axillary lymph node dissection (ALND) in patients with negative SLNB.

Management of Clinically Positive Axilla

A clinically bulky, biopsy/FNAC confirmed that node-positive disease should be managed with ALND.

Management of Positive Sentinel Lymph Nodes

Alliance Z0011 found no difference in local recurrence, DFS, or OS between EBC patients with one or two positive sentinel lymph nodes (SLNs) undergoing a completion ALND versus no ALND. Long-term follow-up (median 9.25 years) results showed no statistically significant difference in local recurrence-free survival between trial arms.[38] cT1-2, N0 tumors, who have not received neoadjuvant therapy, only have one or two positive SLNs, and will undergo BCT may skip complete axillary dissection. If any of the above criteria are not met, complete level I and II axillary dissection are performed. The results of IBCSG 23-01 show that in patients with micrometastases on SLNB, ALND is not required. If there are more than two positive SLNs, we suggest to perform complete ALND.

Management of Axilla Postneoadjuvant Therapy

Patients with initial cN0 disease who remain node negative after neoadjuvant therapy are eligible for SLNB. If sentinel node is negative, these patients (ypN0) do not require completion ALND. In patients with initial node-positive disease, posttreatment SLNB is associated with high false negative rates of 14.2% as per SENTINA,[39] 12.6% as per ACOSOG-Z1071 trial,[40] and 12.6% in the SNFNAC trial.[41] An axillary staging technique that removes any biopsy-proven positive axillary nodes, which are marked with a clip or tattoo prior to neoadjuvant therapy, in addition to SLNB ensure removal of positive nodes while minimizing morbidity. In the Z1071 trial, targeted axillary dissection reduced the false negative rate of SLNB from 12.6 to 6.8% in patients with positive axillary nodes undergoing neoadjuvant treatment.[42] The other techniques to reduce false negative rate are usage of dual agents for lymphatic mapping and identifying three or more SLNs. For patients with any positive sentinel node after neoadjuvant therapy, complete ALND is performed.

Radiotherapy Following Breast Conserving Surgery

Addition of radiotherapy to BCS benefits survival, and reduces the absolute risk of any type of recurrence after 10 years by 15.7% overall and by 15.4% in patients with pN0 disease. Further, the risk of mortality from breast cancer at 15 years reduces by 3.8% overall and by 3.3% for patients with pN0 disease.[43] In pN+ patients, the 10-year recurrence risk and 15-year mortality risk from carcinoma breast are decreased by 21.2 and 8.5%, respectively[44] (►**Table 10**).

Tumor Bed Boost. Ipsilateral breast tumor recurrence (IBTR), which mostly occurs in the proximity of tumor bed, can be as high as 16.4% in the nonboost receiving patients versus 6.4% in the boost group. However, the incidence of skin fibrosis is significantly higher in the boost RT patients. Younger patients benefit the most whereas patients >60 years of age benefit far less.[45]

Accelerated Partial Breast Irradiation. Accelerated partial breast irradiation (APBI) is used as an alternative to whole breast irradiation (WBI) to reduce overall patient visits. Various techniques of APBI include external beam-based APBI (E-APBI), intraoperative radiotherapy (IORT), and interstitial brachytherapy (I-APBI).[46] RTOG 0413/NSABP 39 trial (WBI vs. E-APBI) reported an absolute difference of <1.6% in recurrence-free interval and <1% in incidence of IBTR at 10 years, respectively, but the criterion of equivalence for IBTR incidence was not met. DFS (local and distant) was equivalent for both regimes.[47] Conversely, RAPID and IMPORT LOW trials reported comparable

Table 10 Recommendations for radiotherapy after breast conservation surgery

	LoE	GoR
Postoperative RT is strongly recommended after BCS (I, A)	I	A
Boost RT is recommended to reduce the risk of in-breast relapse in patients: Exceptions are elderly (more than 60 years) with stage I tumors	I	A
APBI is an acceptable treatment option in patients with a low risk for local recurrence	III	C

Abbreviations: APBI, accelerated partial breast irradiation; BCS, breast conservation surgery; RT, radiation therapy; SLNB, sentinel lymph node biopsy.

results for E-APBI versus WBI in obviating IBTR but with slightly worse Grade 2 to 3 late skin toxicity and skin cosmesis.[48,49]

I-APBI is one of the techniques with maximum follow-up and studies have used irradiation dose in the range of 32 to 34 Gy in 8 to 10 fractions by high dose rate (HDR) and 45 to 50 Gy over 4 days by low dose rate (LDR) as both the dose fractionation regimes are radiobiologically equivalent.[46] GEC ESTRO reported an absolute difference in local recurrence between I-APBI and WBI at 0.52% and declared the non-inferiority of the I-APBI arm when compared to WBI.[50] Further, the group compared toxicity and compliance between WBI (with boost) with I-APBI (HDR/pulse dose rate (PDR)) and reported significantly less toxicity (Grade 1–3 skin) in the APBI group.[51]

ELIOT trial (IORT-based APBI) revealed higher rates of IBTR in the IORT group than the conventional group (WBI; 4.4 vs. 0.4%, respectively). The 5-year survival did not differ significantly between the groups. The use of IORT in this trial and others (TARGIT) have demonstrated superiority in long-term cosmesis and toxicity profile but have failed to achieve equivalent ipsilateral recurrence rates.[52]

On the basis of various clinical trials on APBI, patients are staged into low-, intermediate-, and high-risk groups. Patients in the low-risk group are ideal candidates for APBI.[53] It is contraindicated in patients in high-risk group —age <40 years, multicentric disease, lymphovascular invasion (LVI)/extensive intraductal component (EIC) positive, positive margins, pN+ or unknown. In the intermediate-risk group, it should be used with caution. In the low-risk group—age ≥50 years, pT1–2 (<3 cm), unifocal, unicentric, pN0, nonlobular invasive breast cancer, absence of LVI and an EIC, negative surgical margins of at least 2 mm.

Radiation Therapy Following Mastectomy. Despite the increase in use of BCT with equivalent outcomes, mastectomy and axillary dissection is often necessary. Radiotherapy provides no benefit in locoregional recurrence, breast cancer mortality, and overall recurrence in women who undergo mastectomy and adequate axillary dissection with node-negative disease.[54] In an unaddressed or only sampled axilla, the locoregional recurrence is as high as 16.3% and radiotherapy reduces both local and overall recurrences.[55] In node-positive axilla (1–3 nodes,) locoregional recurrence (14% absolute difference between RT and no RT) and breast cancer mortality gets significantly reduced following RT[54,56] (►**Table 11**).

Nodal Radiation Therapy. Axilla must be addressed either via surgery or radiotherapy. RT to nodal basins does not affect survival but improves local and regional recurrences. In patients with cN0/pN0, nodal RT has no effects on outcome and inclusion of nodal fields is not mandatory.[57] Inclusion of nodal RT after mastectomy in pN+ patients leads to drop in recurrences by one-third and deaths in more than one-fifth.[55] Nodal irradiation along with WBI in BCS has also shown an increment in DFS by >20% for pN+ patients.[58] **Internal mammary nodes** (IMNs) inclusion has been a subject of debate for a long time. It may be included in centrally located tumors with considerations to pulmonary and cardiac morbidities. IMN irradiation has been reported to improve survival outcomes.[59] Regional nodal irradiation (RNI) of axilla and supra clavicular fossa (SCF) is strongly recommended in an undissected axilla or in sentinel node positive without complete axillary dissection (►**Fig. 4a, b**). For nodal RT recommendations, please follow ►**Table 12**.

Fractionation Schedules

1. Conventional fractionation: 50 Gy/25 fractions/5 weeks to the chest wall/whole breast with or without nodal basins (I A)
2. Hypofractionation: 40 Gy/15 fractions/3 weeks or 42.5 Gy/16 fractions/3.1 weeks to the chest wall/whole breast with or without nodal irradiation[60] (I, A)
3. Tumor bed boost: conventional fractionation—14 to 16 Gy/7 to 8 fractions or a hypofractionated regimen of 12.5 Gy/5 fractions[61] (III B)
4. APBI: 38.5 Gy/10 fractions/2 fractions a day/1 week or 30 Gy/5 fractions by external body radio therapy (EBRT) (III, C)
5. 34 Gy/10 fractions/2 fractions a day/1 week by balloon/interstitial technique (III C)
6. Fast forward: 26 Gy/5 fractions/1 week to the whole breast/chest wall[62] (III B)

Choice of Adjuvant Endocrine Therapy in Premenopausal Women

Any degree of ER and/or PR positive cases (1% and above) must receive adjuvant hormonal therapy. Genomic tests should be taken into account for guiding treatment decisions in lymph node-negative disease and tumors larger than 0.5 cm. Initial treatment decisions in patients with one to three positive lymph nodes should take into account clinical features, tumor stage, pathology, and the availability and applicability of genetic testing (►**Table 13**).

Table 11 Recommendations for post mastectomy radiotherapy (PMRT)

	LoE	GoR
PMRT is recommended for high-risk patients, including those with involved resection margins, involved axillary lymph nodes, and T3–T4 tumors	I	A
It should also be considered in patients with one to three positive axillary lymph nodes	I	A

Tamoxifen

According to Early Breast Cancer Trialists Collaborative Group (EBCTCG) analysis, adjuvant tamoxifen for 5 years lowers breast cancer mortality by around one-third during the first 15 years following diagnosis and reduces local, contralateral, and distant recurrence of breast cancer by 30 to 50% for the first 10 years. Tamoxifen adjuvant therapy for 10 years has been shown to have a better DFS than therapy for a shorter duration.

Ovarian Function Suppression with Tamoxifen or an Aromatase Inhibitor

The addition of ovarian function suppression (OFS)/ablation to either an AI or tamoxifen for some patients results in a clinically significant reduction in the ROR but increases toxicity. Ovarian function can be suppressed with a gonadotrophin releasing hormone (GnRHa). We define high-risk patients as those in whom chemotherapy is indicated (e.g., patients with

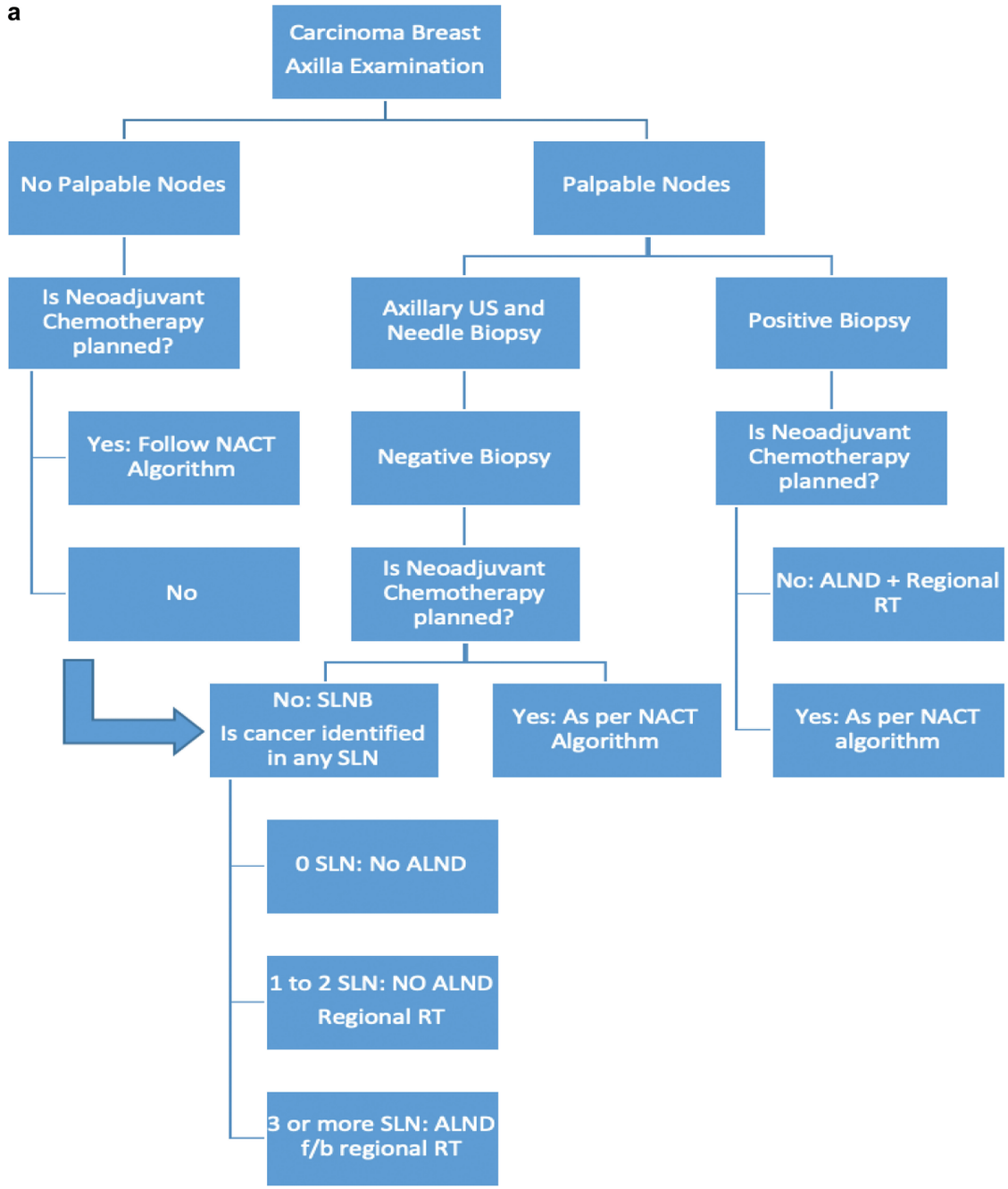

Fig. 4 (a) Algorithm for the role of radiation therapy in early breast cancer. (b) Algorithm for the role of radiation therapy after neoadjuvant therapy. ALND, axillary lymph node dissection; NACT, neoadjuvant chemotherapy; RT, radiation therapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; USG, ultrasound.

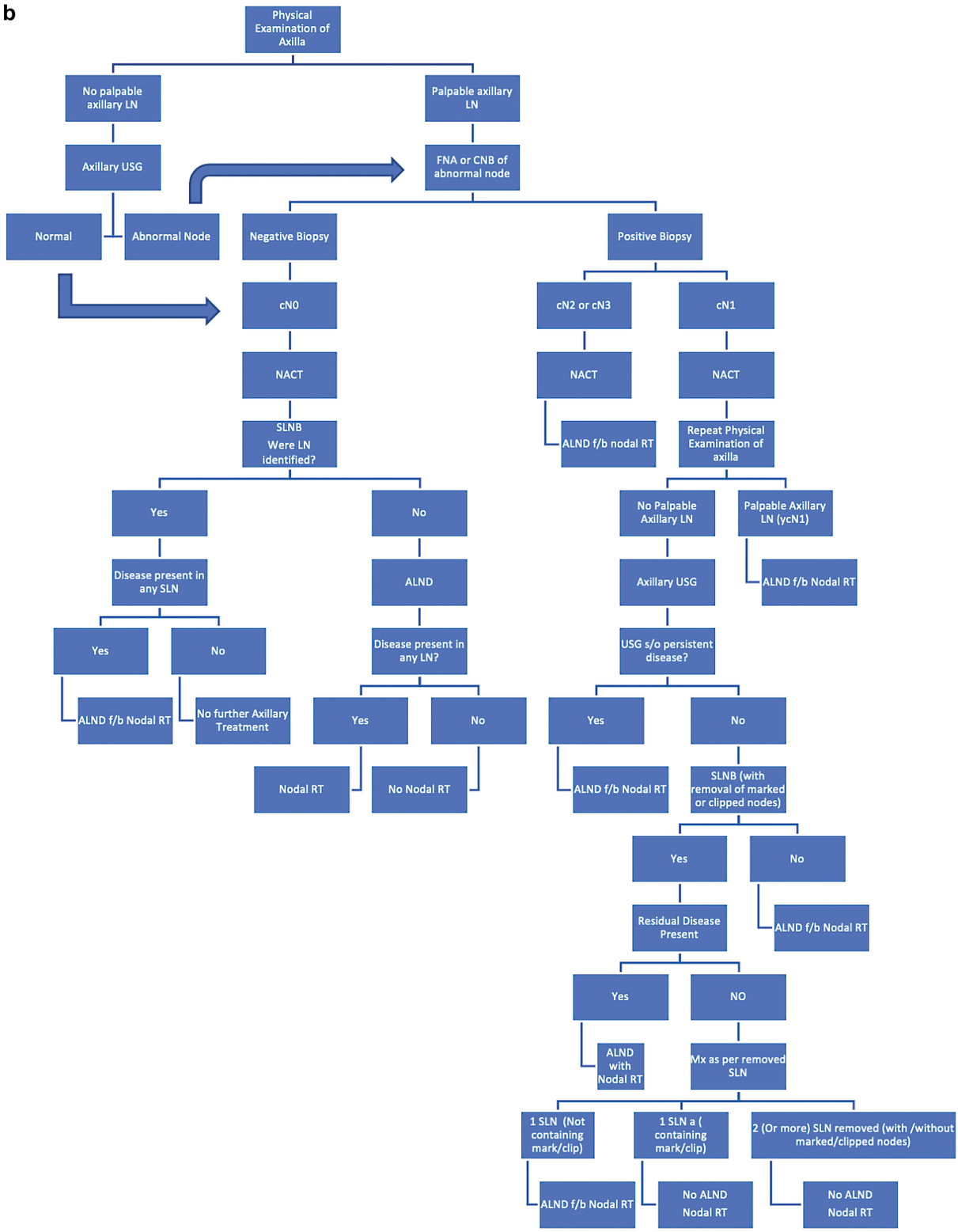

Fig. 4 (*continued*)

Table 12 Recommendations for nodal radiation therapy

	LoE	GoR
Comprehensive nodal RT is recommended for patients with involved lymph nodes	I	B
After ALND, routine axillary irradiation should not be done to the	I	E

Abbreviations: ALND, axillary lymph node dissection; RT, radiation therapy.

Table 13 Choice of adjuvant endocrine therapy in premenopausal women

	LoE	GoR
For premenopausal women, tamoxifen for 5 to 10 years is a standard of care.	I	A
In patients who turn postmenopausal during the first 5 years of tamoxifen, a switch to aromatase inhibitors (AIs) for 2 to 5 years shall be considered, depending on predicted risk of late recurrence.	II	A
In high-risk patients requiring CT (node positive, tumor size more than 2 cm), addition of OFS to ET should be strongly considered.	I	A
OFS during CT provides some protection of ovarian function and has no negative impact on oncological outcomes; thus, it should be proposed to patients. Patients must use barrier contraception along with medical ovarian suppression (recommend monthly LHRH analogs and not 3 monthly)	I	A
Patients undergoing OFS and those taking AIs should be advised to have adequate calcium and vitamin D3 intake and undergo periodic assessment of bone mineral density (by DEXA scan)	I	A

Abbreviations: ET, endocrine therapy; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression.

the presence of pathologically involved lymph nodes [N+], large tumor size [>2 cm], high ROR based on a genomic assay) and young age <35 years. In SOFT trial, tamoxifen plus OFS improved the DFS rate (77 vs. 71%; hazard ratio [HR]: 0.76, 95% CI: 0.60–0.97). Exemestane plus OFS also improved DFS rates (80 vs. 71%; HR: 0.68, 95% CI: 0.53–0.88).[63] OS: tamoxifen plus OFS was associated with an improvement in OS (89 vs. 85%; HR: 0.59, 95% CI: 0.42–0.84). Interestingly, no significant benefit was seen for exemestane plus OFS versus tamoxifen (87 vs. 85%; HR: 0.79, 95% CI: 0.57–1.09).[63] However, the overall conclusions of SOFT are consistent with TEXT for the subset of patients with hormone receptor-positive, HER2-negative disease, which comprised 88% of the overall group (12% had HER2-positive disease).[64]

For women with **high risk**, hormone receptor-positive breast cancer, we suggest incorporation of OFS plus an AI or tamoxifen, rather than tamoxifen alone. When using OFS, we suggest use of an AI rather than tamoxifen. For women with average **low-risk** breast cancer, we suggest tamoxifen as single-agent therapy rather than OFS plus ET. We typically consider low-risk breast cancer to be in women older than 35 years who are without indications for chemotherapy.

Choice of Adjuvant Endocrine Therapy in Postmenopausal Women (►Table 14)

An AI administered instead of or after tamoxifen in postmenopausal women is better to 5 years of tamoxifen alone. According to a meta-analysis of almost 18,000 patients, 5 years of adjuvant AI treatment was linked to a 2.9% absolute decrease in the chance of recurrence and a 1.1% absolute decrease in breast cancer mortality when compared to 5 years of tamoxifen. Patients who received 2 to 3 years of tamoxifen followed by 2 to 3 years of AI experienced reductions in mortality and breast cancer recurrence of 3.1 and 0.7%, respectively, as compared to patients who received tamoxifen alone for 5 years.[65] (►**Table 14**) According to the Intergroup Exemestane Study, patients who switched to an AI after using tamoxifen for the first 2 to 3 years of their treatment regimen and finished 5 years of ET had considerably lower rates of disease recurrence and breast cancer death than those who took the drug for the full 5 years.[66,67] The consecutive use of AIs and tamoxifen was investigated in an EBCTCG meta-analysis of more than 30,000 postmenopausal individuals. AIs were linked to decreased risks of breast cancer recurrence and a 15% reduction in 10-year mortality when 5 years of an AI were compared to 5 years of tamoxifen or to 2 to 3 years of tamoxifen followed by an AI for a total of 5 years. The rates of recurrence for AIs were considerably reduced during years 2 to 4 and the 10-year breast cancer mortality was lower with switching to AIs than with continuing on tamoxifen when 5 years of tamoxifen was compared to 2 to 3 years of tamoxifen followed by AI for a total of 5 years.[68] Postmenopausal women can choose from a number of adjuvant ET alternatives, such as AI for 5 years, AI for 10 years, tamoxifen for 5 years (in the event that AI is contraindicated or poorly tolerated), tamoxifen for 2 to 3 years followed by AI to complete 5 years, or tamoxifen for 5 years followed by AI for 5 years. For women with larger tumors or node-positive disease, we suggest extended endocrine treatment.

Incorporation of Targeted Therapies for Select Patients

Cyclin Dependent Kinase (CDK) 4/6 Inhibitors

We would support the decision to add abemaciclib for 2 years to the existing backbone of adjuvant ET as per monarchE

Table 14 Choice of adjuvant ET in postmenopausal women

	LoE	GoR
For postmenopausal women, AI (both nonsteroidal and steroidal) is the preferred adjuvant therapy. We recommend this treatment for those with hormone receptor-positive breast cancers regardless of size.	I	A
For women receiving adjuvant ET, we recommend at least a 5-year course of treatment.	I	A
For women with higher risk disease (stage II or node positive), we suggest extended endocrine treatment 7 to 10 years, although we recognize that some patients with poor tolerance may choose not to pursue extended treatment.	I	C
For patients receiving adjuvant CT, we initiate ET after CT has completed (i.e., sequentially), in order to minimize toxicities. For women receiving adjuvant radiation therapy (RT) for breast cancer, ET may be initiated concurrently with RT or sequentially, following the completion of RT.	I	A
We recommend addition of abemaciclib to adjuvant ET in high-risk patients.	III	C

Abbreviations: AI, ET, endocrine therapy.

criteria, that is, four or more positive nodes, one to three positive nodes with one of the high-risk feature (ki67 >20%, size more than 5 cm, high-grade disease).[69]

HER2 Breast Cancer: Neoadjuvant and Adjuvant

Neoadjuvant Therapy

All HER2-positive tumors which are more than 2 cm in size or node positive shall be treated with NACT and HER2-targeted drugs, trastuzumab along with pertuzumab. For patients receiving an anthracycline-based regimen as part of their NACT, we typically administer the HER2-targeted therapy concurrently with a taxane, either following completion of or prior to administration of the anthracycline. Patients receiving sequential anthracycline-based chemotherapy and HER2-directed therapy should be monitored closely for cardiotoxicity specially in elderly population.

In Neosphere phase II trial, patients given Pertuzumab, Trastuzumab plus docetaxel had a significantly improved pathological complete response (pCR 45.8%) compared with those given trastuzumab plus docetaxel (29.0%; $p = 0.0141$). The study was not powered to demonstrate the difference in event-free survival as pCR was the primary end point.[70] In the phase III TRAIN-2 trial of 438 patients with stage II to III HER2-positive assigned to anthracycline-containing chemotherapy (three cycles of 5-fluoruoracil, Epirubicin, and cyclophosphamide followed by six cycles of paclitaxel and carboplatin) versus nonanthracycline-based chemotherapy (nine cycles of paclitaxel and carboplatin), with trastuzumab and Pertuzumab administered every 3 weeks with all chemotherapy cycles, the rates of pCR did not differ between the arms (67 vs. 68%). Updated results from this study demonstrate equivalent 3-year event-free (94 vs. 93%) and overall (98 vs. 98%) survival for the anthracycline-free versus the anthracycline-containing regimens, respectively.[71]

Subcutaneous formulations of fixed-dose trastuzumab and pertuzumab are available and are based on similar pCR rates as the intravenous (IV) forms of these therapies. However, the IV formulations were used in all the major trials for both early- and advanced-stage HER2-positive breast cancer.

Adjuvant Therapy

►**Table 15** mentions the level of evidence and grade of recommendation for the usage of anti-HER2 therapy in perioperative setting.

For pT1NO

All patients with less than 2 cm node negative will not have a similar risk of relapse, the risk will significantly increase for size >1 cm, grade 3, hormone-negative tumor. Several retrospective data report recurrence rates as high as 15 to 30% after 5 years for pT1b/c versus pT1a tumors.[72] Curigliano et al analyzed European population of very early (less than 1 cm, node negative) HER2-positive breast cancer. They concluded that tumor size was an independent predictor of 5-year DFS with OR of 2.5 (95% CI: 0.9–6.5; $p = 0.09$). In a European Institute of Oncology[73] population of pT1a/bN0 breast cancers, tumor size was an independent predictor of 5-year DFS with OR of 2.5 (95% CI: 0.9–6.5; $p = 0.09$). Bahl et al[74] published the practical recommendations for the community oncologists in India regarding the use of trastuzumab in early breast cancer. Majority of the experts (70%) agreed that they would offer adjuvant trastuzumab for tumor ≥0.5 cm.

De-escalating Chemotherapy

As we have trials of escalation in the neoadjuvant setting, APT study[75] was the first prospective investigation of a de-escalation of HER2 therapy in the adjuvant setting (weekly paclitaxel and trastuzumab for 12 weeks, followed by completion of 1 year of trastuzumab [H]). A total of 8.9% of these had T size 2 to 3 cm and rest all were less than 2 cm node-negative tumors. The trial met its primary end point with invasive DFS of 98.7% (95% CI: 97.7–99.8) at 3 years, thus supporting an abbreviated chemoregimen for low-risk early HER2-positive disease.

The efficacy and safety of adjuvant T-DM1 in this setting was explored in the ATEMPT[76]: phase II trial of 497 patients with stage I HER2-positive breast cancer were patients were assigned in a 3:1 ratio to T-DM1 versus TH. At a median follow-up of 3.9 years, the 3-year invasive diseases free survival (iDFS) for T-DM1 was 97.8% (95% CI: 96.3–99.3) versus 93.4% (95% CI: 88.7–98.2) with TH. Since 17% receiving T-DM1 discontinued for adverse events and the concerns over limited follow-up of patients in this trial puts T-DM1 as

Table 15 Choice of anti-HER2 therapy

	LoE	GoR
All HER2-positive tumors which are more than 2 cm in size or node positive shall be treated with neoadjuvant chemotherapy and HER2-targeted drugs	I	A
We consider six cycles of taxane–carboplatin–trastuzumab (with or without pertuzumab) regimens as preferable alternatives to anthracycline-containing regimens (4AC or 4EC followed by weekly paclitaxel) as neoadjuvant therapy	I	A
SC formulations are reasonable alternatives to IV formulations for both trastuzumab and pertuzumab	III	B
For all pT1b/c, we recommend adjuvant chemotherapy/trastuzumab. For patients with pT1a tumors, **we advise adjuvant chemotherapy/trastuzumab for 4- to 5-mm tumor if they are hormone negative** (►**Fig. 1**)	II	B
For women with pT1b/c N0, we suggest to use weekly Paclitaxel for 12 weeks along with Trastuzumab for 1 year	II	A
One year of (neo) adjuvant trastuzumab remains a standard for the vast majority of HER2-positive patients but in select subgroup,[a] shortening trastuzumab duration to 6 months shall be discussed	I	A
For patients who had residual invasive disease after completion of neoadjuvant chemotherapy with anti-HER2 therapy (Trastuzumab with or without pertuzumab), substitute adjuvant trastuzumab with trastuzumab emtansine (T-DM1) for 14 cycles	II	B
For those with pathologic complete response following HER2-directed therapy, we recommend adjuvant trastuzumab to complete a year of HER2-directed therapy	III	B
For those with node-positive breast cancer, who have not received any neoadjuvant therapy, **we advise trastuzumab with pertuzumab** along with chemotherapy	II	B

Abbreviations: AC, Anthracycline/Cyclophosphamide; IV, intravenous; SC, subcutaneous.
[a]Low risk: hormone negative, node negative, elderly with cardiac comorbidities.

not a standard adjuvant regimen for small, HER2-positive tumors.

De-escalating Trastuzumab Duration

Though the standard duration of adjuvant Trastuzumab is 1 year, there have been trials with shorter duration (9 weeks/6 months) which have shown discordant results. Manuprasad et al[77] in a retrospective study from South India gave 9 weeks of Trastuzumab due to financial constraints along with 4 AC (doxorubicin + cyclophosphamide), weekly paclitaxel 12, as chemotherapy backbone. One hundred and twenty-nine patients received short-course trastuzumab and majority of these patients ($n = 120$, 93%) had T1/T2 disease and were node-negative ($n = 62$, 57%). At a median follow-up of 29 months, the 3-year OS was 98%; the median OS was not reached. The 3-year DFS was 97.4%; the median DFS was not reached.

Gulia et al[78] analyzed individual patient data for DFS and OS from six eligible randomized control trials (RCTs) including data from PHARE and Persephone trials. The noninferiority margin chosen was based on the margins in the included RCT (1.3; range: 1.15–1.53). For shorter duration versus 1 year of trastuzumab, the 5-year DFS was 85.42 versus 87.12% (HR: 1.14; 95% CI: 1.03–1.25, one-sided p-value for noninferiority =0.004), and OS was 92.39 versus 93.46% (HR: 1.17; 95% CI: 1.02–1.33). There was significantly less risk of congestive heart failure with shorter duration trastuzumab (relative risk, 0.53; 95% CI: 0.38–0.74).

Escalation of Anti-HER2 Therapy

In Katherine trial,[79] 1,486 women with HER2-positive early breast cancer with residual invasive disease after NACT plus HER2-directed therapy (trastuzumab with or without pertuzumab), were included. These patients when randomized in adjuvant setting to 14 cycles of T-DM1 versus trastuzumab, improved 3-year invasive DFS (88 vs. 77%; HR: 0.50, 95% CI: 0.39–0.64) for TDM1 arm. Although the DFS improved with postoperative TDM-1 in patient on neoadjuvant doublet HER2 therapy (trastuzumab + pertuzumab), it was not significant (HR: 0.54, 95% CI: 0.27–1.06). Extended adjuvant anti-HER2 therapy with neratinib in patients who completed 1 year of trastuzumab demonstrated additional improvement in DFS, in particular in the ER-positive subgroup, albeit at the cost of significant toxicity, mostly diarrhea.

APHINITY,[80] a phase III trial randomized 4,800 patients with node positive or high risk, node negative, operable breast cancer to chemotherapy and trastuzumab with either pertuzumab or placebo. At a median follow-up of 8.4 years, invasive diseases free survival (IDFS) was 88.4 versus 85.8% (2.6% difference) in the intention to treat (IIT) population (►**Fig. 5**).

Chemotherapy for Early-stage Triple-Negative Breast Cancer

Patients with triple-negative breast cancer (TNBC) require adjuvant chemotherapy with Anthracycline/Cyclophosphamide (AC) and taxane-based chemotherapy delivered sequentially is the standard of care. The prognosis of node-negative, triple-negative tumors ≤0.5 cm is generally favorable, and therefore, the benefits of adjuvant chemotherapy are likely to be very small and must be weighed against the chances of side effects of chemotherapy. Dose-dense

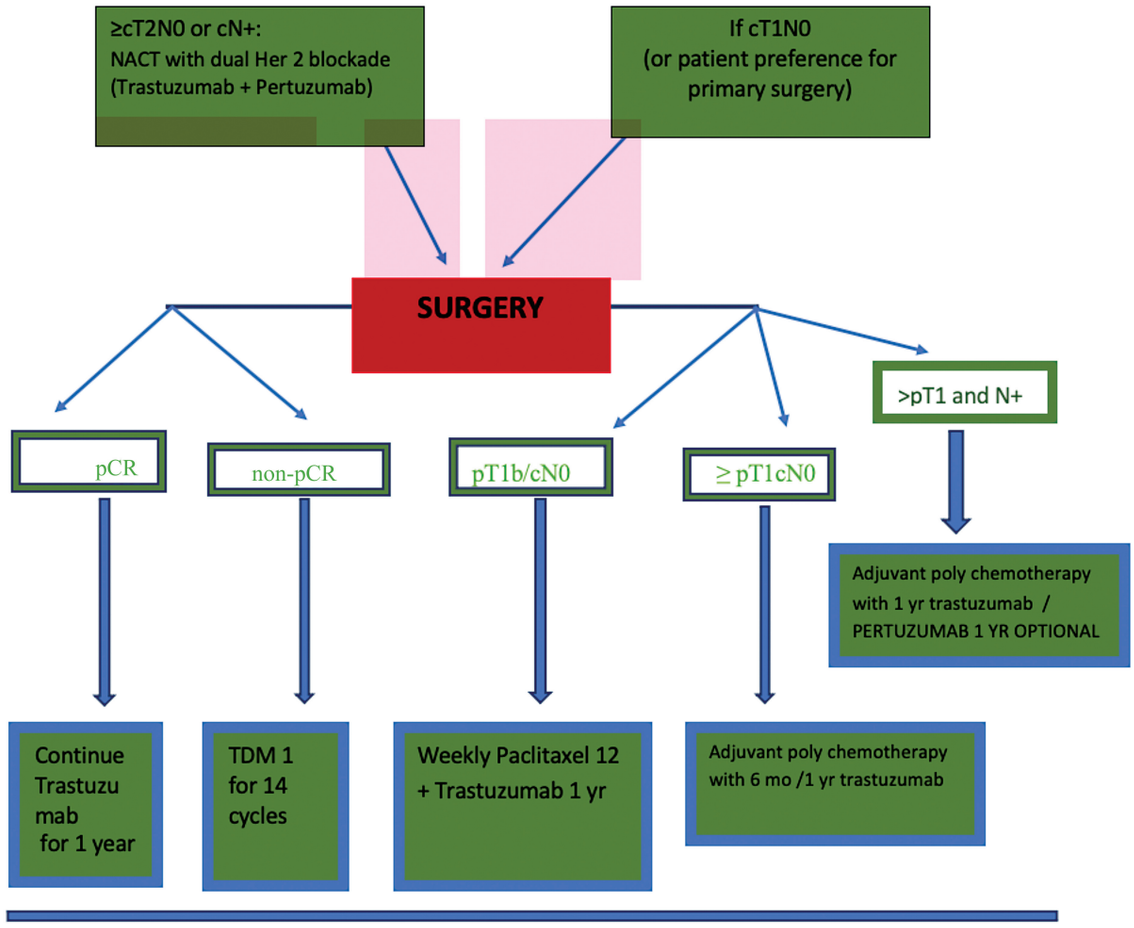

Fig. 5 Treatment algorithm for neoadjuvant therapy for HER2-positive EBC. pCR, yr, year.

chemotherapy regimens given once in 2 weeks in the adjuvant setting have shown an OS benefit over three weekly regimens.[81] However, dose-dense regimens are associated with increased toxicity, especially febrile neutropenia, therefore, patients must be monitored closely and receive prophylactic filgrastim granulocyte colony stimulating factor (GCSF) support, especially during AC chemotherapy (►**Table 16**).

Table 16 Recommendations for role of triple-negative breast cancer in early breast cancer

	LoE	GoR
Patients with triple-negative breast cancer (TNBC; >0.5 cm)/node-positive require adjuvant chemotherapy	I	A
AC/Taxane-based dose-dense chemotherapy is preferred for high-risk TNBC (more than 2 cm, node positive)	I	A
Clinicians can individualize the decision to add Carboplatin to the chemotherapy regimen along with taxane.	I	C
NACT does not offer a survival advantage in operable TNBC	II	A
Carboplatin can be considered along with paclitaxel in neoadjuvant therapy to increase the pCR in BRCA1/2 patients	I	C
Patients who do not achieve pCR after NACT should be treated with eight cycles of adjuvant capecitabine postoperatively	I	C
Pembrolizumab for the treatment of patients with high-risk, early-stage TNBC[b] in combination with chemotherapy as neoadjuvant treatment, and then continued pembrolizumab as a single agent as adjuvant treatment after surgery for 1 year.	I	B
Patients with a germline *BRCA* mutation: Olaparib is approved for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA* mutation, HER2-negative, high-risk early breast cancer.[b]	I	A

Abbreviations: AC, Anthracycline/Cyclophosphamide; NACT, neoadjuvant chemotherapy; pCR, pathological complete response.
[b]High-risk early triple-negative breast cancer: more than 2 cm, node positive.

A nonanthracycline-based regimen like docetaxel and cyclophosphamide (TC) for four cycles is not recommended in early-stage TNBC due to the disease's aggressive nature. Evidence suggests that anthracycline-based chemotherapy is superior to six cycles of TC in high-risk (TNBC, grade 3, tumor >2 cm, and node positive) early breast cancer.[82] The panel recommends dose-dense AC for 4 cycles followed by weekly paclitaxel for 12 cycles as the standard of care in early-stage TNBC. A nonanthracycline-based regimen can be used in patients in whom anthracyclines are contraindicated due to cardiac morbidities. A three-drug combination regimen containing 5-Flurouracil is not recommended.

Role of Platinum in Triple-Negative Breast Cancer

Platinum chemotherapy has shown increased effectiveness in TNBC (significant rise in pCR), especially in BRCA mutants. A recent meta-analysis showed that adding platinum in neoadjuvant and adjuvant settings improves survival in TNBC.[83] Gupta et al[84] randomized 720 patients with TNBC to four doses of adriamycin cyclophosphamide/weekly paclitaxel for eight doses with and without weekly carboplatin for eight doses. At a median follow-up of 67.6 months, the 5-year DFS (primary end point) was 70.6% for carboplatin arm and 64.5% without carboplatin (HR: 0.79, 95% CI: 0.61–1.02, $p = 0.073$). In subgroup analyses for women <50 years of age in experimental versus control arms, 5-year DFS and OS were 74.5 versus 62.3% ($p = 0.003$, interaction $p = 0.003$) and 76.8 versus 65.7% ($p = 0.003$, interaction $p = 0.004$), respectively. The panel's consensus is that the physician shall individualize the decision to add carboplatin to paclitaxel in early-stage TNBC, majorly for premenopausal (less than 50 years).

Indications for Neoadjuvant Chemotherapy

The benefits of NACT in early breast cancer include assessing response in the surgical specimen, which has a prognostic significance, pathological CR-guided adjuvant treatment and downsizing of the tumor to facilitate BCS. We would recommend using NACT in TNBC with more than 2 cm or node-positive disease. The planned cycles' NACT should be delivered before surgery. The regimens used in the adjuvant setting are also used in the neoadjuvant setting. To increase the pathological complete response rate (pCR), adding carboplatin to neoadjuvant paclitaxel might be considered in patients with BRCA1 or 2 mutations.[85] Patients who do not achieve pCR after NACT should be treated with eight cycles of adjuvant capecitabine postoperatively.[86]

In the phase III KEYNOTE-522[87] trial, patients with early-stage, high-risk TNBC, Anthracycline, Taxane and Carboplatin-based chemotherapy with and without Pembrolizumab were administered in the neoadjuvant setting. Pembrolizumab was continued in the adjuvant setting for a total of 1 year duration. Immunotherapy was found, regardless of PD-L1 status, for patients with a T2 or higher and/or node-positive breast cancer to improve both pathologic complete response and event-free survival. For patients who also have germline *BRCA* mutations, 1 year of adjuvant Olaparib, a poly-ADP ribose polymerase (PARP) inhibitor, decreases the ROR and increases OS of patients, as shown in the OlympiA[88] phase III trial.

Treatment of Elderly Patients

(►**Table 17**) Most treatment guidelines for elderly patients limit their recommendations to being applicable to biologically older patients, need for use of a formal validated geriatric assessment tool and avoidance of standard "aggressive" regimens in frail elderly. India (and other South Asian Association Regional Cooperation (SAARC) as well as Low and Middle Income Countries (LMIC) countries) face additional challenges. Most Indian patients will depend on someone else (younger, main breadwinner for the family) to make their treatment decision—often based on family circumstances. Geriatric assessment tools developed and validated in the western world are inappropriate to capture the aspects important to elderly Indians, especially with respect to cultural differences and beliefs.[89] Screening of the older person with cancer is a step in the right direction for our country.[90] In one large study, it was able to identify functional impairment in 75% of the cases, two or more comorbidities in 64%, and malnutrition in 35% of patients.

On the other hand, the benefit that the standard adjuvant systemic therapy can provide should not be denied to geriatric patients because it is similar to that seen in younger patients with early breast cancer. In addition, Indian patients with breast cancer, including those with early breast cancer, often have higher expression of poor prognostic genes.

The challenge therefore, is to provide optimal treatment without compromising quality of life (especially avoiding all kinds of toxicities). For instance, use of AIs in the elderly is associated with significantly higher risk of fractures, a complication that could result in premature death. Identifying

Table 17 Recommendations for elderly patients

	LoE	GoR
Treatment of elderly early breast cancer patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used	II	B
A geriatric assessment should be carried out before making treatment decisions in all patients more than 65 years	II	A

Abbreviation: ChT, Chemotherapy.

high-risk patients will limit appropriate adjuvant therapy to the subset that can really benefit from it; at the same time preventing unnecessary medication (including logistics, loss of earning for caregiver, potential toxicities) to the majority.

Bone-modifying Agents in Early Breast Cancer

Preserving bone health in breast cancer is an integral part of the treatment to alleviate the bone loss caused by ovarian suppression/hormone therapies and to improve breast cancer outcomes. The bone-modifying agents (BMAs) include bisphosphonates and the receptor activation of nuclear kappa B ligand inhibitor, Denosumab. Various schedules have been used such as 6-monthly zolendronic acid for 5 years (Z FAST and ZO-FAST[91] study) versus 6-monthly for 3 years (ABCSG-12 Study[93]).

The EBCTCG meta-analysis of data pooled from 18,000 women from 26 trials including the AZURE and ABCSG-12 validate the survival benefit of adjuvant bisphosphonates in EBC but only for postmenopausal patients with a significant benefit by reducing recurrence (Risk ratio (RR) = 0.86, $2p = 0.002$), distant recurrence (RR = 0.82, $2p = 0.0003$), and breast cancer mortality (RR = 0.82, $2p = 0.002$) which is independent of tumor grade, hormone receptor (HR) and HER2 receptor status, chemotherapy, and the bisphosphonate class. The nonbreast cancer mortality was unchanged.[93] Recently published are the contradictory survival outcomes of the two randomized phase III RCT ABCSG-18[94] and D-Care[95] using denosumab which led to the recommendation against the use of adjuvant denosumab. **We thus favor use of zoledronic acid over denosumab in adjuvant setting.**

Please refer to ►**Table 18** for recommendations regarding the use of BMAs in nonmetastatic breast cancer.

Pregnancy-associated Breast Cancer and Breast Cancer after Pregnancy

Pregnancy-associated breast cancer (PABC) includes breast cancer diagnosed during pregnancy (BCP) or postpartum.[96,97] However, they merit separate categorization.

The BCP management demands multidisciplinary, precision care and depends upon disease stage, receptor status, gestational age, and performance status.[98–102]

Delayed diagnosis is common and to reduce such delays, clinical and self-breast examination, and obstetricians' awareness to investigate a breast lump during pregnancy are required.[11] Chest X-ray, ultrasound of the abdomen and pelvis, and a noncontrast skeletal MRI are recommended staging investigations.[100,102,103] Histopathology is a must to confirm diagnosis with documentation of receptor status for therapeutic and prognostic importance.

BCP management essentially mirrors the standard breast cancer management with careful considerations towards pregnancy trimesters and safety of mother and fetus.[99,101,103] Pregnancy termination generally has not found to improve outcomes and not recommended unless there are pressing obstetric and/or oncologic reasons. The treatment outcomes varies, however, stage and biology-matched outcomes are found comparable in many studies including the first Indian gestational registry by Bajpai et al, wherein a total of 104 PABC cases over 7 years has also shown comparable oncological and obstetrical outcomes.[98] Prematurity was found as an important negative prognosticator for cognitive development and hence avoidance of iatrogenic preterm deliveries are recommended, unless there are pressing obstetric reasons.[100,101]

The positive trail[103] supports the data of temporary interruption of ET in 516 women with more than 90% having stage I/II disease. Among 497 women, 74.0 and 63.8% had at least one pregnancy and live birth, respectively. The 3-year incidence of breast cancer events was 8.9% (95% CI: 6.3–11.6) in the treatment-interruption group and 9.2% (95% CI: 7.6–10.8) in the control cohort. At present, in select women with proper counseling, patients with HR+ disease should complete at least 18 to 24 months of ET with a wash off period of 3 months before attempting pregnancy (if they cannot wait till completion of ET).

Pregnancy after breast cancer can be considered even in those with HRs and/or BRCA mutation-positive disease under trained oncology professional care. There are sparse data on breastfeeding after BC. Patients who continued having systemic therapy should not breastfeed. Other women can breastfeed and should be counseled appropriately by professionals.

►**Table 19** mentions the level of evidence and recommendations for PABC.

Treatment of Male Breast Cancer

Male breast cancer (MBC) is a rare disease comprising only 1% of all breast cancers.[104] However, the incidence of MBC has been rising over the past few decades.[105,106] Usually, MBC resembles its much more common female counterpart in many ways but there are some differences—the cancer is diagnosed at an elderly age, has high node positivity, and high rate of ER positivity.[107] The vast majority of breast cancer cases in male patients are ductal invasive carcinomas of the luminal-like type (►**Table 20**).

Table 18 Recommendations for bone-modifying agents

	LoE	GoR
Bisphosphonates for early breast cancer are recommended in women with low estrogen status (undergoing OFS or postmenopausal), especially if at high risk of relapse (I, A).	I	A
Zoledronic acid six monthly for 2 to 5 years is recommended in patients with treatment-related bone loss	I	A
Denosumab is not recommended in the adjuvant setting	II	B

Abbreviation: OFS, ovarian function suppression.

Table 19 Recommendations for pregnancy-associated breast cancer and breast cancer diagnosed during pregnancy

	LoE	GoR
Standard chemotherapy (Anthracyclines/Taxane-based) can be offered to the majority considering the tumor stage and biology after first trimester. Adriamycin is preferred over epirubicin.	Expert opinion	
Other systemic therapy including **endocrine therapy, trastuzumab, immunotherapy, and bone-modifying agents should be avoided in all trimesters.**	I	A
There are sparse data on breastfeeding after BC. Patient on systemic therapy postdelivery should not breastfeed.	Expert opinion	
Surgery can be considered in second (preferred) or third trimester.	III B	

Abbreviation: BC, breast cancer.

Table 20 Recommendations for male breast cancer

	LoE	GoR
ChT and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients	IV	A
Tamoxifen is the standard adjuvant ET for male breast cancer patients	IV	A
If a strong contraindication exists for the use of tamoxifen, a combination of an AI plus a luteinizing hormone-releasing hormone agonist may be considered, but its higher toxicity must be discussed with the patient to avoid compliance issues	IV	B
An AI alone should not be used as adjuvant ET in male breast cancer patients	IV	E

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy.

Follow-up and Survivorship in Early Breast Cancer

The purpose for regular follow-up in patients with early breast cancer is manifold. This aims

- to detect early recurrences, both local, contralateral and distant;
- to evaluate and manage long-term treatment-related complications related to adjuvant hormonal therapy such as osteoporosis, menopausal symptoms, and second malignancies;
- to motivate and encourage patients to continue and complete adjuvant hormonal therapy;
- to address psychosocial concerns and offer information for dealing with these issues so as to establish a new normal.

Five-year OS rate of breast cancer in India ranged from 40 to 62%.[108] The results from 16 publications showed that survival of breast cancer varies widely depending on number of factors like age, stage at diagnosis, marital status, educational level, hormonal status, clinical extent of disease, and treatment.

Table 21 Recommendations for follow-up

	LoE	GoR
Regular follow-up visits are recommended every 3 to 4 months in the first 2 years (every 6 months for low-risk and DCIS patients), every 6 to 8 months from years 3 to 5 and annually thereafter.	V	A
Annual bilateral (after BCT) and/or a contralateral mammography (after mastectomy), with USG when needed is recommended	II	A
In asymptomatic patients, other laboratory or imaging tests (e.g., blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, CT scans, FDG-PET-CT) or any tumor markers such as CA15-3 or CEA are not recommended	I	D
Regular bone density once every 1 to 2 years is recommended for patients on AI or undergoing OFS	I	A
Patients should be encouraged towards adopting a **healthy lifestyle, including diet modification, exercise, yoga, and weight reduction**	II	A
Hormone replacement therapy for ameliorating menopausal symptoms among survivors should usually not be used	I	D
Long-term survivorship issues (psychological needs and issues related to work, family and sexuality) should be addressed	V	A

Abbreviations: AI, aromatase inhibitor; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; OFS, ovarian function suppression; USG, ultrasound.

Although there are no randomized data to support the efficacy of a particular follow-up schedule, it is important to address patient needs during follow-up posttreatment.

During a follow-up visit, it is important to extract a detailed history with a special emphasis on new and troublesome symptoms and a physical examination. Mammography (digital preferred) ± ultrasound should be performed annually. In young patients with dense breasts and hereditary breast cancer, MRI would be beneficial. There are no data to suggest that additional CT and PET scan tumor markers or even chest X-rays have any survival benefit and should not be routinely performed. Tests to monitor side effects of hormonal therapy may be carried out. These include pelvic ultrasound to assess endometrial thickness in women on tamoxifen and lipid profile and bone density for those on AIs.

Modification of lifestyle factors has been shown to reduce the ROR in early breast cancer. Recommendation of regular exercise should be made to all patients.[109] Weight gain and obesity contributes to worse prognosis as does Hormone replacement therapy (HRT).[110,111] Specialized rehabilitation services like management of lymphedema and arm exercises are also important for recovery.

Follow-up clinics should address the psychosocial aspects of survivorship in women with early breast cancer, with a special focus on mental well-being, work-related issues, family, and sexual needs.

In summary, a survivorship plan is important to include aspects of long-term follow-up care and can be developed including the points mentioned above. This is relevant to our context as it is estimated that there are over 1.5 million breast cancer survivors in India at present.

Refer to ►**Table 21** for recommendations on follow-up after treatment for breast cancer survivors.

Authors' Contributions

S.A., A.S., R.S. contributed in Concept, Design and Intellectual content whereas S.G., P.K., S.A. reviewed the manuscript. All authors were involved in Literature search, Clinical studies, Data analysis, Manuscript preparation and Editing.

Conflict of Interest

None declared.

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Comparison of Efficacy and Safety of Talc to Povidone-Iodine Pleurodesis in Malignant Pleural Effusion: A Systematic Review and Meta-Analysis

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Ind J Med Paediatr Oncol 2025;46:24–30.

Abstract

Malignant pleural effusion (MPE) poses a substantial clinical challenge, necessitating effective interventions. Pleurodesis, commonly employed in MPE management, involves inducing pleural symphysis to prevent fluid accumulation. Talc and povidone-iodine have emerged as prominent agents for pleurodesis, each with its unique characteristics and considerations. This systematic review and meta-analysis aimed to compare the efficacy and safety of talc powder pleurodesis (TPP) and povidone-iodine pleurodesis (PIP) in the management of MPE. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic review registered in PROSPERO (CRD42023470930). Randomized controlled trials (RCTs) with TPP and PIP arms for MPE were included. The information sources included electronic bibliographic databases such as PubMed, Scopus, Web of Science, Cochrane, and Embase from inception to November 2023. The Cochrane risk of bias tool was used for the critical appraisal. A meta-analysis using RevMan 5.3 compared outcomes. Out of 105 identified records, 3 RCTs were included in our review. Our review findings revealed a higher success rate for TPP. However, variability existed, with one study indicating better success rates in PIP groups. Adverse events were reported less frequently in the PIP group, suggesting a potentially superior safety profile. TPP showed higher overall success in comparison to PIP, emphasizing the need for cautious clinical decision-making given variability. The potential superior safety profile of povidone-iodine underscores the importance of context-specific choices, considering patient preferences and resource constraints in selecting pleurodesis interventions for MPE management.

Keywords

- malignant pleural effusion
- talc pleurodesis
- povidone-iodine pleurodesis
- efficacy
- safety

article published online
November 29, 2024

DOI https://doi.org/10.1055/s-0044-1796636.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Malignant pleural effusion (MPE) poses a substantial challenge in clinical settings, requiring effective interventions to alleviate its symptoms and prevent its recurrence.[1] Pleurodesis, a common therapeutic approach, aims to induce pleural symphysis to prevent fluid accumulation due to MPE, recurrent pneumothorax, and some nonmalignant effusions. It involves chemical agents or physical abrasion during thoracotomy or thoracoscopy. The ideal agent for pleurodesis should be highly effective, having specific characteristics, yet none meet all the criteria, prompting ongoing research.[2]

Talc is widely used despite a lack of consensus on the best agent. Though effective for MPEs, concerns about talc-related acute respiratory distress syndrome arose but were later challenged.[2] Cost and availability limit medical-grade talc use, particularly in resource-poor countries. Povidone-iodine, an affordable antiseptic, proved safe and effective for pleurodesis in prior studies.[1,2]

Talc and povidone-iodine have emerged as prominent agents for pleurodesis in MPE management due to their efficacy and safety profiles.[1,3] Talc pleurodesis (TP), employing sterile talc powder, has long been considered a gold standard due to its high success rates in achieving symphysis and preventing effusion recurrence.[1] Povidone-iodine, an iodophor solution, has gained attention as a potential alternative to talc, this attention is attributed to povidone-iodine having higher efficacy, lower cost, and easy availability compared with talc.[1] Numerous studies have examined the efficacy, safety, and outcomes of these two agents concerning pleurodesis.[1,3,4] TP and povidone-iodine pleurodesis (PIP) have been evaluated for their effectiveness in managing MPE.[2,5] The debate primarily revolves around their comparative effectiveness, safety profile, recurrence rates, and cost-effectiveness in treating MPE. Studies have compared the outcomes and safety aspects of both interventions.[1,3] The comparison between talc and povidone-iodine in pleurodesis is crucial in resource-limited settings due to cost implications. Studies highlight povidone-iodine as a potentially cost-effective alternative to talc.[2] If both agents exhibit comparable efficacy in treating MPE, opting for povidone-iodine could be advantageous.[1,3] Povidone-iodine's lower cost and easy availability make it appealing, especially in areas with limited resources.[1] The potential to achieve similar therapeutic outcomes while minimizing expenses might notably benefit health care systems facing constraints in funding or availability of resources.

Materials and Methods

Registration and Protocol

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the findings.[6] The study protocol was registered in PROSPERO: International Prospective Register of Systematic Reviews (registration number: CRD42023470930) before conducting the study.

Objectives

The research question for the systematic review is "What are the comparative efficacy and safety of TP and PIP in the management of MPE?" The research question was broken down into (population, intervention, comparison, and outcome) PICO format. The defined "population" was patients with MPE, without restriction on age, sex, and ethnicity. "Intervention" was patients treated with TP, whereas "comparator" was patients treated with PIP. The "outcome" measures assessed were efficacy and safety.

Eligibility Criteria

The studies were considered eligible to be included according to the following criteria.

Inclusion Criteria

(1) Interventional studies that include both TP and PIP in MPE patients.

Exclusion Criteria

(1) Interventional studies that include a study arm involving either TP or PIP with some other comparators; Any study lacking TP and PIP interventions will be ineligible for consideration.
(2) Animal studies.
(3) Nonretrievable articles or abstract-only papers.

Information Sources and Search Strategy

We have critically reviewed the literature to select relevant articles published in the electronic bibliographic databases from inception until December 30, 2023. We systematically performed an advanced electronic search in PubMed, Scopus, Web of Science, Cochrane, and Embase for eligible studies. The search strategy in the above database was performed using the keywords and Medical Subject Headings (MeSH) terms like "malignant pleural effusion," "Pleurodesis," "povidone iodine," "talc," using "AND" and "OR" (►**Supplementary File S1**, available in the online version). We limited the search to English publications.

Study Selection Process and Data Extraction

The studies were screened by title and abstracts followed by full-text articles based on predefined criteria. Two independent reviewers (D.B. and T.B.) performed the study selection, and disagreements were resolved by mutual consultation with a third reviewer (M.K.M). A well-defined data extraction sheet was employed for data extraction. Data from the final selected studies included authors' names, year of publication, study design, sample size, study groups, clinical outcomes, and adverse effects. One reviewer (T.B.) extracted the data in a standardized extraction sheet, and the other reviewer (D.B.) checked for accuracy. Any disagreement was resolved by a mutual discussion or consultation with a third reviewer (M.K.M).

Risk of Bias Assessment

The Cochrane risk of bias assessment tool was used to assess the methodological quality of the included studies.[7] Two

independent reviewers (D.B. and T.B.) performed the quality assessment, and any disagreements between the reviewers were settled through consensus or discussion with a third reviewer (M.K.M.).

Data Synthesis

A narrative synthesis was performed from the extracted data findings and presented in tabular form. The data synthesized in the review summarized the current evidence of efficacy and safety for TP and PIP in MPE. Subgroup analysis could not be performed due to insufficient available data.

Statistical Analysis

We used the Review Manager software (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Oxford, United Kingdom) to conduct a meta-analysis, and odds ratio (OR) with 95% confidence interval (CI) values was calculated.[8] Statistical heterogeneity of data was assessed using the I^2 statistic, and the fixed-effects model was used for studies without significant heterogeneity ($I^2 \leq 50\%$ or $p \geq 0.10$). We could not create a funnel plot for assessing visual inspection of publication bias due to a lack of sufficient eligible studies.

Results

Study Selection

We identified 105 records by searching the MeSH terms from the abovementioned databases. We removed 54 duplicate records before the screening, leaving 51 unique records for further assessment. Out of these, 43 records were excluded, indicating the stringent application of predefined inclusion/exclusion criteria. Subsequently, efforts were made to retrieve eight reports for closer evaluation, although only six reports were successfully obtained and assessed for eligibility. Within this assessment, four reports were excluded, comprising two conference abstracts, one trial protocol, and one observational study that did not meet the desired comparator criteria. We employed a manual search strategy that resulted in the identification of two records. Subsequently, reports sought for retrieval and reports assessed for eligibility both amounted to two records each. However, one report was excluded due to being in a language other than the specified language criterion. Finally, we incorporated a total of three studies in the review.

Study Characteristics

All the final selected studies were randomized controlled trials (RCTs). We identified all research papers by the first author's last name and year (►**Table 1**). In tabular format, we recorded the extracted data from the three studies.[1,3,4] Among the included studies, two were conducted in Egypt[1,3] and one was conducted in India.[4] We extracted data from a study group consisting of patients with MPE who underwent pleurodesis with either povidone-iodine or talc. The flowchart for study selection according to the PRISMA guidelines is shown in ►**Fig. 1**. Among the three included studies, Agarwal et al had conducted their study by taking either benign or MPE.[4] Hence, according to our review criteria, we have extracted data about MPE only.

Overall Efficacy

To compare the efficacy of TP and PIP procedures, we identified and extracted the data on outcome measures, which were in terms of success rate, complete inflation, partial inflation, and failure rate (►**Table 2**).

Success Rate

In Ibrahim et al, the success rate was found to be 80.85% (17 out of 21) and 72.22% (13 out of 18) in the TP and PIP groups, respectively.[1] Similarly, Mohsen et al reported the success rate to be 90.90% (20 out of 22) and 85% (17 out of 20) in the TP and PIP group, respectively.[3] In the case of Agarwal et al, the success rate was high in the case of PIP. The success rate was reported to be 90% (16 out of 18) and 95% (17 out of 18) in the TP and PIP groups, respectively.[4]

Complete Inflation

Ibrahim et al[1] found the complete inflation to be high in the TP group, that is, 71.43% (15 out of 21) than in the PIP group, that is, 66.66% (12 out of 18). In the case of Mohsen et al,[3] the rate of complete inflation was almost similar, which was 86.36% (19 out of 22) and 85% (17 out of 20) in the TP and PIP groups, respectively.

Partial Inflation

The partial inflation rate was reported to be 9.52% (2 out of 21) and 5.55% (1 out of 18) in the TP and PIP groups, respectively, in Ibrahim et al.[1]

Failure Rate

Ibrahim et al reported the failure rate to be 19.04% (4 out of 21) and 27.77% (5 out of 18) in the TP and PIP groups, respectively.[1] A similar trend was observed by Mohsen et al, which was 9.09% (2 out of 22) and 15% (3 out of 20) in the TP and PIP groups, respectively.[3]

Adverse Events

To compare the occurrence of adverse events between the TP and PIP groups, we extracted the relevant data from the

Table 1 Characteristics of selected studies

Author/Year [Ref]	Regions	Study design	Study duration	Population
Ibrahim et al, 2015[1]	Egypt	RCT	Not available	Recurrent MPE
Mohsen et al, 2011[3]	Egypt	RCT	January 2002 to December 2005	MPE
Agarwal et al, 2011[4]	India	RCT	January 2006 to June 2007	MPE

Abbreviations: MPE, malignant pleural effusion; RCT, randomized controlled trial.

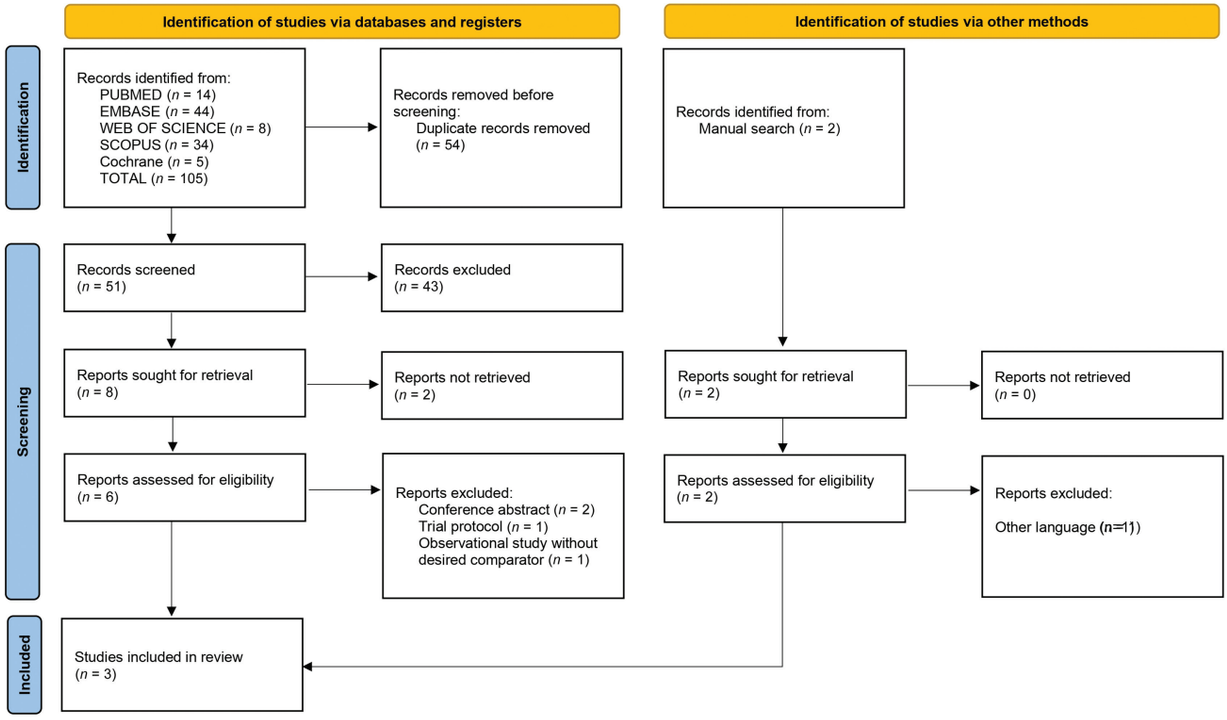

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the screening and selection process.

selected studies for postprocedure pain, fever, recurrence of dyspnea, allergy, and death (►**Table 3**).

In the TP group, Ibrahim et al reported 66.66% (14 out of 22), 19.04% (4 out of 21), and 19.04% (4 out of 21) for pain, fever, and recurrence of dyspnea, respectively.[1] Whereas in the PIP group, 50% (9 out of 18), 22.22% (4 out of 18), and 27.77% (5 out of 18) for pain, fever, and recurrence of dyspnea, respectively. There were no adverse events reported for allergy and death in any of the pleurodesis groups.[1]

Mohsen et al reported 18.18% (4 out of 22) for pain and fever in TP.[3] They had reported for fever in 5% (1 out of 20) of the PIP group. There were no adverse events reported for pain and recurrence of dyspnea in the PIP group.[3]

Along with the above adverse events Mohsen et al reported the postprocedure hospital stay and mean survival rate among pleurodesis patients. The postprocedure hospital stay was reported to be 5.7 ± 2 and 4.5 ± 1.1 days in the TP and PIP groups, respectively. The mean survival rate was higher in the PIP group, which was 33.8 months, compared with TP, which was 27.7 months.[3]

Risk of Bias within the Studies

The methodological quality assessment of all three studies has been mentioned in ►**Table 4**. We have conducted the quality assessment for Cochrane risk of bias focused on the following domains: random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases.

We have omitted the two domains: blinding of participants and personnel as well as blinding of outcome assessment. Given the inherent differences in the interventions being studied, blinding of participants and personnel is challenging. Specifically, the TP intervention necessitates thoracoscopy, whereas the PIP intervention does not involve this procedure. Consequently, the nature of the interventions makes it impractical to blind participants and personnel to the treatment assignment due to the distinctive procedural requirements associated with each intervention.

The risk of bias in the mentioned domain in all included studies was categorized according to the following: high risk of bias, low risk of bias, unclear risk of bias, and not applicable.

Meta-Analysis

The success rate of TP was compared against PIP among MPE patients. ►**Fig. 2** represents the summary results of pooled data from all three RCTs on success rate.[1,3,4] The fixed-effect model was considered because of the lack of statistical heterogeneity among studies ($I^2 \leq 50\%$ or $p \geq 0.10$). The pooled analysis of the three studies having a total of 117 MPE patients showed a nonsignificant OR of 1.31 (95% CI: 0.46–3.72). The resulting I^2 value of 0% suggests that any heterogeneity might not be important among the included studies, which could be due to a small number of participants.[1,3,4]

Discussion

Our systematic review aimed to compare the efficacy and safety of TP versus PIP in managing MPE. We found that TP demonstrated a higher success rate in achieving pleurodesis than PIP.[1,3] However, one of the studies included in the

Table 2 Overall efficacy between talc pleurodesis and povidone-iodine pleurodesis

Study	Number of participants		Success rate		Complete inflation		Partial inflation		Failure	
	Talc, *n*	Povidone-iodine, *n*	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)
Ibrahim et al, 2015[1]	21	18	17 (80.85)	13 (72.22)	15 (71.43)	12 (66.66)	02 (9.52)	01 (5.55)	04 (19.04)	05 (27.77)
Mohsen et al, 2011[3]	22	20	20 (90.90)	17 (85%)	19 (86.36%)	17 (85%)	01 (4.54%)	00 (0%)	02 (9.09)	03 (15)
Agarwal et al, 2011[4]	18	18	16[a] (90)	17[a] (95)	.	.	.	.	.	.

[a]Calculated from the given percentage value and total no. of participants in Agarwal et al.

Table 3 Adverse events between talc pleurodesis and povidone-iodine pleurodesis

Study[Ref]	Pain		Fever		Recurrence of dyspnea		Allergy		Death	
	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)
Ibrahim et al, 2015[1]	14 (66.66)	09 (50)	04 (19.04)	04 (22.22)	04 (19.04)	05 (27.77)	00 (0)	00 (0)	00 (0)	00 (0)
Mohsen et al, 2011[3]	04 (18.18)	00 (0)	04 (18.18)	01 (5)	00 (0)	.	.	.	.	.
Agarwal et al, 2011[4]	.	.	.	.	.	.	.	.	.	.

Table 4 Cochrane risk of bias assessment for selected studies

Studies[Ref]	Sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias
Ibrahim et al, 2015[1]	Low	High	Low	Low	Low
Mohsen et al, 2011[3]	Low	Low	Low	Low	Low
Agarwal et al, 2011[4]	Low	Low	Low	Low	Low

analysis presented differing results, leading to variability in findings.[4] While both interventions were generally well-tolerated, adverse events like pain and fever were reported less frequently in the povidone-iodine group, suggesting a superior safety profile for povidone-iodine. The clinical importance of these findings lies in the similar outcomes of TP and PIP in providing effective and sustained relief for patients with MPE. However, it is essential to consider the small sample size in all the included studies, which may impact the generalizability of these results. A retrospective observational study by Makkar et al showed a 79% success rate in pleurodesis with manageable pain and minimal complications.[9] In a meta-analysis, Muthu et al suggested that povidone-iodine is a cost-effective and widely available alternative, with a success rate of approximately 90%.[10] Their findings revealed no notable adverse effects like thyroid dysfunction or iodine toxicity, at standard doses. While talc poudrage may be superior according to a network meta-analysis, tube thoracostomy with povidone-iodine remains a practical option, especially in resource-constrained settings.[11] Another meta-analysis by Beltsios et al noted the potential superiority of TP over other mechanical approaches.[5] Comparatively better success rate associated with TP suggests that it may be a preferred option for more robust and sustained pleurodesis in patients with MPE. Clinicians may consider TP as a first-line intervention, particularly in cases where long-term efficacy is a primary concern. However, the superior safety profile of PIP, with fewer reported adverse events, presents an important alternative, especially in situations where minimizing complications is a priority. Clinicians should weigh the potential benefits of effective pleurodesis against the safety considerations when selecting the appropriate intervention for individual patients. Our findings align with the study by Muthu et al supporting the role of povidone-iodine as a cost-effective and widely available alternative with a pooled success rate of 90%.[10] A recent comprehensive review conducted by Bonser et al concluded that the current standard of care for pleurodesis in MPE is based on limited evidence.[12]

The study limitations hinder the generalizability of recommendations. However, the available evidence suggests that povidone-iodine is a safe, well-tolerated, and equally effective agent for achieving palliative pleurodesis in MPE. Povidone-iodine has several advantages including low cost, accessibility, and ease of administration, making it a suitable alternative to talc in certain clinical settings.[12] In resource-constrained settings, where talc may pose logistical challenges, povidone-iodine emerges as a practical option without compromising efficacy. Clinicians must consider the local context, patient preferences, and available resources when making decisions about pleurodesis interventions. While TP may be favored in settings with adequate resources and expertise, PIP can be a valuable alternative in situations where logistical constraints or safety concerns are paramount. The choice between TP and PIP should be made through shared decision-making involving the patient, considering individual factors such as comorbidities, treatment goals, and preferences. Additionally, ongoing monitoring for adverse events, patient response, and the need for repeat procedures should be integral components of post-pleurodesis care, irrespective of the chosen intervention. This nuanced understanding of the comparative effectiveness and safety profiles of TP and PIP should inform evidence-based decision-making in the clinical management of MPE. However, this systematic review has certain limitations. The primary constraint lies in the small sample size of the included studies, which may limit the generalizability of the findings. Additionally, variations in, the type of malignancy, and follow-up durations across the three RCTs might have influenced the heterogeneity. Also, including studies reporting no significant statistical differences between TP and PIP could have influenced the pooled results. However, their inclusion was necessary to reduce publication bias and provide a more balanced

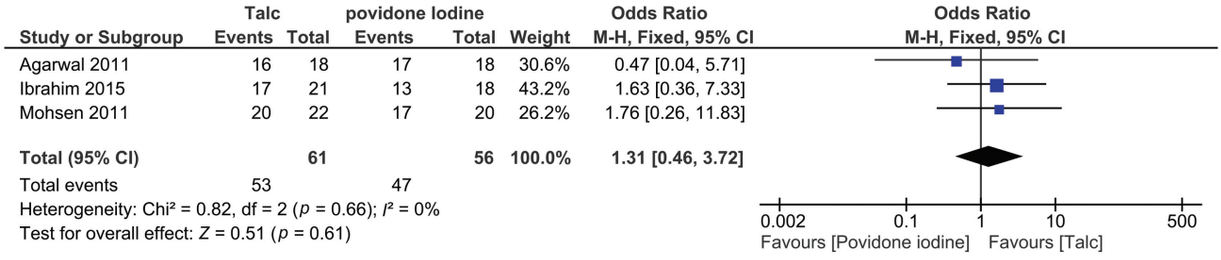

Fig. 2 The success rate in talc pleurodesis versus povidone-iodine pleurodesis.

and comprehensive analysis of the available studies on TP versus PIP in MPE patients. These warrant need for a larger, greater number of studies to strengthen the evidence base for informed clinical decision-making.

Future Directions

Future research should concentrate on conducting well-designed multicenter RCTs with larger sample sizes. Standardization of study protocols, including consistent outcome measures, will enhance the comparability of results across trials. Additionally, exploring patient-specific factors that may influence the choice of pleurodesis agent and conducting long-term follow-up studies are critical steps in advancing our understanding of the comparative effectiveness of TP and PIP. These may help to develop a prediction model for point care for MPE.

Conclusion

Although TP is more effective in achieving pleurodesis, the PIP treatment appears to have a better safety profile with fewer adverse effects. The importance of these results is that both treatments provide effective and long-lasting relief for patients with MPE. However, further research is needed, including larger and more standardized trials, to build on these findings and refine treatment guidelines in this clinical context.

Authors' Contributions

D.B. conceptualized the review question. D.B. and T.B. did the systematic search, data extraction, and risk of bias assessment. D.B. and T.B. interpreted the extracted data. T.B. performed the meta-analysis. D.B. and T.B. wrote the manuscript. M.K.M., S.S.M., and A.K.M. critically evaluated the manuscript. All the authors approved the final draft of the article.

Patient Consent

None declared.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

None.

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Outcome of CBV (Carmustine, Cyclophosphamide, Etoposide) Conditioning Regimen for Autologous Stem Cell Transplant in Lymphoma: A Retrospective Study from a Tertiary Cancer Center in South India

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Ind J Med Paediatr Oncol 2025;46:31–39.

Abstract

Introduction In autologous stem cell transplant (ASCT) for lymphomas, no standard conditioning regimen has been defined so far. Thus, the choice is guided by the center's familiarity and experience with a particular regimen.

Objective To determine the response, toxicity, and survival outcomes in lymphoma patients who underwent ASCT with CBV (cyclophosphamide, carmustine, and etoposide) conditioning regimen.

Materials and Methods Between January 2013 and May 2019, 45 consecutive lymphoma patients who had ASCT with CBV conditioning regimen were included in this retrospective study. CBV consisted of cyclophosphamide (1.5 g/m^2/day $\times$ 4 days), carmustine (300 mg/m^2 $\times$ 1 day), and etoposide (125 mg/m^2 twice daily $\times$ 3 days). Baseline characteristics, pre transplant response, apheresis, post-transplant toxicities, post-transplant response, and survival outcomes were collected. Endpoints were toxicity, response, event-free survival (EFS), and overall survival (OS).

Results The median age was 30 (range: 6–64) years. Diagnosis was Hodgkin lymphoma (HL) in 26 (58%) and non-Hodgkin lymphoma (NHL) in 19 (42%). Forty-three patients (95%) had chemosensitive disease; 22(49%) in CR, and 21 (46%) in PR. The median CD34 was 2.95×10^6/kg (range: 0.9–9.56). The median time to neutrophil engraftment was 11 days (9–23) and 13 (8–36) days for platelets. All patients had febrile neutropenia, clinically and/or microbiologically documented infection was seen in 75% of patients. The most common grade 3/4 toxicities were mucositis ($n = 4$, 9%), diarrhea ($n = 4$, 9%), and nausea/vomiting ($n = 2$, 4%). The average days of hospitalization was 18 (range: 10–37). Day 100 mortality was 6.6% ($n = 3$). The median follow-up was 44.8 months. The median EFS for the entire cohort was 23.8 months; for HL, the median EFS was not reached, and for NHL, it was 7.97 months (95% confidence interval [CI]: 1.57–14.37). The median OS for the

Keywords
- CBV conditioning regimen
- autologous stem cell transplant
- Hodgkin lymphoma
- non-Hodgkin lymphoma

article published online
February 2, 2022

DOI https://doi.org/10.1055/s-0041-1740134.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

entire cohort and for HL was not reached; for NHL, it was 24.3 months (95% CI: 0.56–48.11).

Conclusion CBV conditioning regimen was well tolerated with low grade 3/4 toxicities and efficacy comparable to literature data.

Introduction

High-dose chemotherapy (HDC) followed by autologous stem cell transplant (ASCT) is the current standard of care for relapsed/refractory lymphoma.[1,2] Several HDC regimens with varying drug combinations, with or without total body irradiation (TBI), have been in use as the conditioning protocol in autologous transplant of lymphomas. Most have shown similar efficacy but different toxicity profiles. Compared to chemotherapy-TBI regimens, chemotherapy-only regimens have demonstrated superiority in terms of disease-free survival (DFS), overall survival (OS), and lesser toxicity.[3,4] Commonly used HDC regimens in ASCT for lymphoma include BEAM (BCNU, etoposide, cytarabine, and melphalan), BEAC (BCNU, etoposide, cytarabine, and cyclophosphamide), CBV (cyclophosphamide, BCNU, and etoposide), and LACE (lomustine, etoposide, cytarabine, and cyclophosphamide),[5–9] but no prospective randomized study has been done so far comparing these regimens. Most of the retrospective studies comparing various HDC regimens have shown variability in toxicity, and some have reported differences in disease outcomes.[3,10–16]

In our center, CBV has been the commonest conditioning regimen used for autologous transplant in lymphomas. Unfortunately, data regarding the use of CBV are scant in contemporary published literature, and there are no reports on the use of CBV conditioning from India. This study has retrospectively analyzed the toxicity profile, engraftment kinetics, and survival outcomes of lymphoma patients who have undergone ASCT using a CBV conditioning regimen.

Methodology

Patient Population

From January 2013 to May 2019, all consecutive histology-proven relapsed or refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) patients, who had a complete or partial response to salvage chemotherapy and underwent ASCT at our center, with CBV conditioning regimen were included in this retrospective study. Patients who received other conditioning regimen were excluded from the study.

We collected the data for baseline characteristics, pre-transplant response, apheresis, post-transplant toxicities, post-transplant response, and survival outcomes from medical records maintained in the department. Endpoints were toxicity, post-transplant response, event-free survival (EFS), and overall survival (OS).

Pre-Transplant Assessment

Relapsed or refractory lymphoma was treated with 3 to 4 cycles of first- or second-line salvage chemotherapy depending on their primary diagnosis and previous treatment history. Post salvage response assessment was done with either contrast-enhanced computed tomography (CECT) scan or positron emission tomography and computed tomography (PET-CT) scan. Pre-transplant chemosensitivity was defined as either complete or partial response following salvage therapy. Evaluation was done for organ functions (renal, hepatic, cardiac, and pulmonary) and general fitness as per the department protocol for all patients prior to transplant.

Stem Cell Mobilization, Collection, and Cryopreservation

Peripheral blood (PB) stem cell mobilization was done with GCSF 5 µg/kg twice daily for 4 days. One day prior to apheresis, on the fourth day of mobilization, PB CD34 enumeration was done. Plerixafor was used 12 hours before apheresis if the PB CD34 was <20 cells/mm^3 or as per physician's discretion based on the baseline risk factors for poor mobilization. All patients had undergone peripheral blood stem cell (PBSC) harvest by apheresis, and stem cell enumeration was done at the end of harvest. PBSC collected were volume depleted and cryopreserved using 10% of dimethyl sulfoxide (DMSO) and autologous plasma at –80° C until day 0 (day of stem cell reinfusion).

Conditioning Regimen

CBV conditioning regimen was given over a period of 6 days in the following schedule: BCNU (carmustine) 300 mg/m^2 intravenous (iv) over 2 hours on D-6, cyclophosphamide 1.5 g/m^2/day i.v. over 2 hours on D-6 to D-3, mesna 120% of cyclophosphamide dose as i.v. infusion over 24 hours on D-6 to D-3, and 40% of cyclophosphamide dose as i.v. infusion over 12 hours on D-2, etoposide 125 mg/m^2/dose i.v. over 1 hour 12th hourly on D-6 to D-4. The above CBV schedule is considered as CBV (low) compared to the older regimen CBV (high), which used carmustine at 600 mg/m^2.[10,11]

Supportive Care

All patients received G-CSF 5 µg/kg/day subcutaneous (s.c.) starting on day +1 after stem cell infusion until the absolute neutrophil count (ANC) was greater than 0.5×10^9/L for least 3 days.[17,18] Irradiated packed red cell concentrates and platelet concentrates were given to keep hemoglobin >8.0 g/dL and platelet count $>20 \times 10^9$/L, respectively. Oral fluconazole and acyclovir were started from day 1 as antifungal

and antiviral prophylaxis, respectively. Routine antibacterial prophylaxis was not given. Total parenteral nutrition (TPN) was administered in patients who developed grade 3–4 mucositis and in any grade mucositis with decreased food intake. Febrile neutropenia was managed as per the department antibiotic policy.

Study Definitions

Time to neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count of $\geq 0.5 \times 10^9$/L.[19,20] Time to platelet engraftment was defined as the first of three consecutive days when the platelet count was maintained $\geq 20 \times 10^9$/L without platelet transfusion.[19] Engraftment syndrome was defined by the presence of noninfectious fever and one other symptom (i.e., skin involvement, diarrhea, or pulmonary manifestations) during the peri-engraftment period.[21] Regimen-related organ toxicities, evaluated in the first 100 days, were graded using the Seattle criteria, whereas mucositis and chemotherapy-induced nausea and vomiting (CINV) were graded using the National Cancer Institute Common Terminology Criteria For Adverse Events (NCI CTCAE) v4.0.[22,23] The length of hospital stay (LOS) was defined as the time from the day of infusion of stem cell product (Day 0) to the day of hospital discharge. Transplant-related mortality (TRM) was defined as any death not related to relapse or disease progression during the first 100 days after the transplant. EFS (event-free survival) was defined as the time interval from the date of the transplant to disease progression, relapse, or death due to any cause. Overall survival (OS) was defined as the time from transplant to death due to any cause or date of the last follow-up.

Statistical Analysis

Descriptive statistics were used to summarize baseline disease features, pre-transplant disease status, patient characteristics, and post-transplant outcomes. Estimation of EFS and OS was done using the Kaplan–Meier method and compared using log rank test. Data were censored on 31 March 2020 for survival analysis. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM was used for analysis.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. The study was approved by the Institute Ethics committee (no. JIP/IEC/2016/30/979, dated 23.10.2016), and waiver of informed patient consent was granted.

Results

Baseline Characteristics and Pre-Transplant Data

During the study period, 45 patients (28 males and 17 females) underwent autologous transplant with a CBV conditioning regimen for refractory/relapsed lymphoma. The median age was 30 years (range: 6–64). Diagnosis was HL in 26 patients (58%) and NHL in 19 patients (42%). Of the 45 patients, 28 (62%) had relapsed after their primary treatment, and 15 (35%) had refractory disease. The median time from diagnosis to transplant was 19 months, and median lines of previous therapy were two. As a part of pretransplant response assessment, PET CT and CECT was done in 22 (49%) and 23 (51%) patients, respectively. Among the 45 patients, 43 (96%) had chemosensitive disease (either complete response [CR] or partial response [PR]). All patients had ECOG (Eastern Cooperative Oncology Group) performance status of 1 before transplant baseline clinical characteristics, and pre-transplant disease status is shown in ►**Table 1**.

Apheresis

For 45 patients, a total of 70 apheresis procedures were done. The median number of apheresis done was 2 (range: 1–3); for HL was 2 (range: 1–3), and for NHL was 1 (range: 1–3). The median CD34 cells/kg for entire cohort was 2.95×10^6/kg (range: 0.9–9.56), for HL 2.99×10^6 (range: 0.90–7.3), and for NHL 2.90×10^6 (range: 1.77–9.56). The median total MNC/kg for the entire cohort was 6.04×10^8 (range: 2–27), for HL 6.03×10^8 (range: 2–27), and for NHL 6.35×10^8 (range: 4–20). All PBSC apheresis products were cryopreserved and stored at –80°C until the day of infusion.

Conditioning Regimen and Post-Transplant Outcomes

All 45 patients received a CBV conditioning regimen without any modifications. The median day to neutrophil engraftment and platelet engraftment was 11 days (range: 9–23) and 13 days (range: 8–36), respectively. Five patients had engraftment syndrome, and all responded to low-dose steroids. All patients had febrile neutropenia, of which 11 (24%) had an FUO (fever of unknown origin) while others had either a CDI (clinically documented infection), MDI (microbiologically documented infection), or both CDI and MDI. The median day to the onset of fever was 2 days (range: 0–11). The median number of antibiotics used was 4 (range: 1–8), and median days of antibiotic usage was 14 (range: 6–29) days. Empirical antifungal, amphotericin B was used in 15 patients (33%).

Grade 3–4 mucositis was seen in four patients, and all received total parenteral nutrition. Grade 3/4 diarrhea and CINV (chemotherapy-induced nausea and vomiting) were observed in four and two patients, respectively. Hypokalemia and hypomagnesemia were seen in 18 (40%) and 11 (25%) patients, respectively. None of the patients had hemorrhagic cystitis, and no grade 3/4 toxicity was observed in other organs viz. renal, liver, pulmonary, or cardiac. The median duration of stay in the transplant unit was 18 days (range: 10–37). Transplant-related mortality (TRM) at 100 days was 6.6% ($n = 3$; HL, 1 and NHL, 2), the cause of death being severe sepsis for all patients. One patient died before engraftment on d + 20, and two patients died after engraftment on d + 26 and d + 78. ►**Table 2** presents the data on engraftment kinetics, pattern of infection, and toxicity post-transplant.

Post-Transplant Response

The post-transplant response was available for 40 (89%) patients. Post-transplant response assessment was not done in five patients as three died before d + 90, and two

Table 1 Baseline clinical, treatment characteristics and pre-transplant disease status in HL and NHL

Features		Entire Cohort ($N = 45$)	HL ($N = 26$)	NHL ($N = 19$)
Age (at transplant) in years		30 (6–64 years)	26 (6–47)	38 (19–64)
Gender Male Female		28 (62.2%) 17 (37.8%)	17 (65%) 9 (35%)	11 (58%) 8 (42%)
Diagnosis (lymphoma)			26 (58%)	19 (42%)
Relapsed		28 (62%)	14 (54%)	14 (74%)
Refractory		15 (34%)	12 (46%)	3 (16%)
Upfront (in CR1 for HR)		2 (4%)	–	2 (10%)
NHL	Relapsed/refractory DLBCL	–	–	12 (63%)
	ALCL (ALK negative) (upfront)			2 (11%)
	Relapsed FL			2 (11%)
	Relapsed PTCL			1 (5%)
	Relapsed AITL			1 (5%)
	Relapsed ALCL			1 (5%)
Time from diagnosis to transplant in months (median, range)		19 (5-102)	21 (8–84)	16 (5–102)
Number of lines of treatment (median, range)		2 (1–4)	2 (1–4)	2 (1–3)
ECOG PS (median, range)		1 (0–1)	1 (0–1)	1 (0–1)
Chemosensitivity				
Yes		43 (95.6%)	24 (92%)	19 (100%)
No		2 (4.4%)	2 (8%)	0
Pre-transplant imaging for disease status PET CT-22 (49%) CECT–23 (51%)				
PET CT response ($N = 22$)				
CR (complete response)		15 (68%)	10 (77%)	5 (55%)
PR (partial response)		7 (32%)	3 (23%)	4 (45%)
SD (stable disease)		0	0	0
PD (progressive disease)		0	0	0
CECT response ($N = 23$)				
CR (complete response)		8 (35%)	5 (39%)	3 (30%)
PR (partial response)		13 (56%)	6 (46%)	7 (70%)
SD (stable disease)		1 (4.5)	1 (7.5%)	0
PD (progressive disease)		1 (4.5%)	1 (7.5%)	0

Abbreviations: AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; CECT, contrast-enhanced computed tomography; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group-Performance status; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PET CT, positron emission tomography and computed tomography; PTCL, peripheral T cell lymphoma.

were lost to follow-up post-ASCT. In the entire cohort, post-transplant CR was observed in 25 (62.5%) patients, PR in 8 (20%) patients, and progressive disease (PD) in 7 (17.5%) patients. Change in the disease status from pre-transplant period to post-transplant is shown in the bar diagram in ►**Fig. 1**.

Survival

The median follow-up for the entire cohort was 44.8 months (95% CI: 33.8–55.8). The median EFS for the entire cohort was 23.8 months (95%CI: 0.00–63.68); for HL, the median EFS was not reached, and for NHL, it was 7.97 months (95%CI: 1.57–14.37). Estimated 3-year EFS was 48% for the entire cohort; for HL and NHL, it was 57.4% and 33.7%, respectively. The median OS for the entire cohort and for HL was not reached; for NHL, it was 24.3 months (95%CI: 0.56–48.11). The estimated OS at 3 years was 61.6% for the entire cohort and 74.6% and 43.4% for HL and NHL, respectively.

An association of survival outcomes with respect to baseline features viz. relapsed vs. refractory disease, number of lines of salvage therapy, and pre-transplant disease status, complete response vs. partial response is shown in

Table 2 Post-transplant engraftment kinetics, pattern of infection, toxicity, and supportive care in HL and NHL

		Entire cohort ($N = 45$)	HL ($N = 26$)	NHL ($N = 19$)
Day of engraftment	Neutrophils	11 (9–23)	11 (9–17)	10.5 (9–23)
	Platelets	13 (8–36)	12.50 (8–36)	14.5 (11–30)
Febrile neutropenia	FUO	11 (24%)	8 (31%)	3 (16%)
	CDI	18 (40%)	9 (35%)	9 (47%)
	MDI	10 (22%)	5 (19%)	5 (26%)
	CDI and MDI	6 (14%)	4 (15%)	2 (11%)
No of antibiotics		4 (1–8)	4 (2–8)	4 (1–7)
Organism	Sterile	26 (58%)	15 (58%)	11 (58%)
	Gram negative	13 (30%)	6 (23%)	7 (37%)
	Gram positive	0	0	0
	Polymicrobial	5 (10%)	5 (19%)	0
	Fungal	1 (2%)	0	1 (5%)
Mucositis	Grade 0	10 (22%)	3 (10%)	7 (37%)
	Grade1–2	31 (69%)	19 (76%)	12 (63%)
	Grade 3–4	4 (9%)	4 (14%)	0
CINV	Grade 0	9 (20%)	4 (16%)	5 (26%)
	Grade 1–2	34 (66%)	20 (77%)	14 (74%)
	Grade 3–4	2 (4%)	2 (7%)	0
Diarrhea	Grade 0	21 (47%)	13 (50%)	8 (42%)
	Grade 1–2	20 (43%)	10 (38%)	10 (53%)
	Grade 3–4	4 (10%)	3 (12%)	1 (5%)
TPN	Yes	4 (9%)	4 (15%)	–
	No	41 (91%)	22 (85%)	19 (100%)
Blood products	PRBC	3 (0–8)	3 (0–8)	3 (0–7)
	SDP	4 (2–13)	4 (2–12)	4 (2–13)
Length of stay in days (median, range)		18 (10–37)	25 (10–37)	18 (10–30)

Abbreviations: CDI, clinically documented infection; CINV, chemotherapy-induced nausea and vomiting; FUO, fever of unknown origin; HL, Hodgkin lymphoma; MDI, microbiologically documented infection; NHL, non-Hodgkin lymphoma; PRBC, packed red blood cells; SDP, single donor platelets; TPN, total parenteral nutrition.

►**Supplementary Tables S1** and **S2**. A comparison of survival outcomes based on the pre-transplant disease status of CR vs. PR in subgroups of HL and NHL, respectively, is shown in ►**Fig. 2**.

Discussion

The present standard of care for relapsed/refractory lymphoma is HDC followed by ASCT.[2,5] Several HDC regimens have been in use as conditioning protocol in the autologous transplant of lymphomas, and most have shown similar

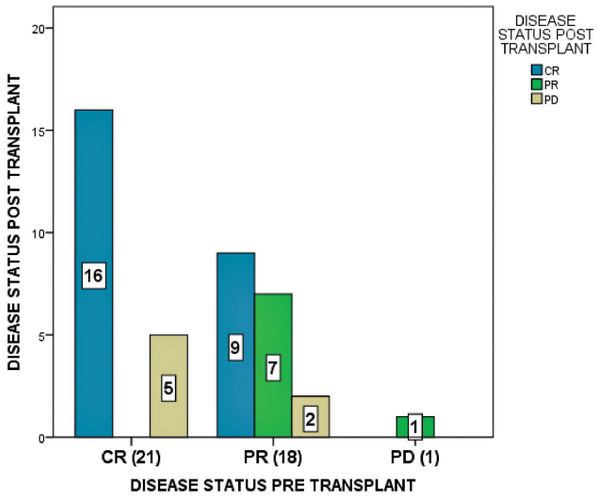

Fig. 1 Comparison of disease status pre and post-transplant in the entire cohort; CR, complete response, PR, partial response, PD, progressive disease. X axis indicates disease status pre-transplant and Y axis indicates disease status post-transplant. Among 21 patients who had CR pre transplant, 16 maintained CR, and 5 had progressive disease post-transplant. Among the 18 patients who had PR before transplant, 9 achieved CR, 7 maintained PR, and 2 had progressive disease. One patient who had progressive disease pre transplant achieved PR post-transplant.

efficacy but with different toxicity profiles. CBV is one of the older conditioning regimens for lymphoma with a relatively safer toxicity profile, especially with low-dose CBV. Sparse data are available on the contemporary use of CBV, especially from India. Our study found CBV practicable, less toxic, and had efficacy comparable to that reported in the literature for other regimens used in lymphoma conditioning.

We report the results of 45 transplants for HL and NHL with CBV conditioning. The majority of the patients (95%) had chemosensitive disease at transplant. Grade 3 or 4 toxicities were observed in only 10% of our patients, common toxicities being mucositis, diarrhea, and CINV. No grade 3/4 toxicity was observed in other organs viz. renal, liver, pulmonary, or cardiac. Toxicity in our study was comparable to that reported for low-dose CBV.[10,11,16] Studies with the original CBV (high dose) regimen with BCNU dose of 600 mg/m^2 have reported higher pulmonary toxicity (5–10%). However, subsequent reports with the use of BCNU at 450 mg/m^2 or 300 mg/m^2 (CBV low) have shown less pulmonary toxicity (<1%) without any loss of efficacy.[10–12,16] Also, Chen et al proved that carmustine dose higher than 300 mg/m^2 resulted only in increased toxicity without any survival benefit.[10] Other grade 3 or 4 toxicities with CBV (low) included mucositis in about 8 to 25%, diarrhea 10 to 25%, CINV 4 to 8% from various studies in the literature.[10,14,16] As summarized in ►**Table 3**, grade 3/4 regimen-related toxicities were relatively less with CBV (low) compared to other commonly used conditioning regimens such as BEAM, BEAC, or LACE (10–25% in CBV low vs. 30–55% in other regimens) although with comparable survival outcomes.

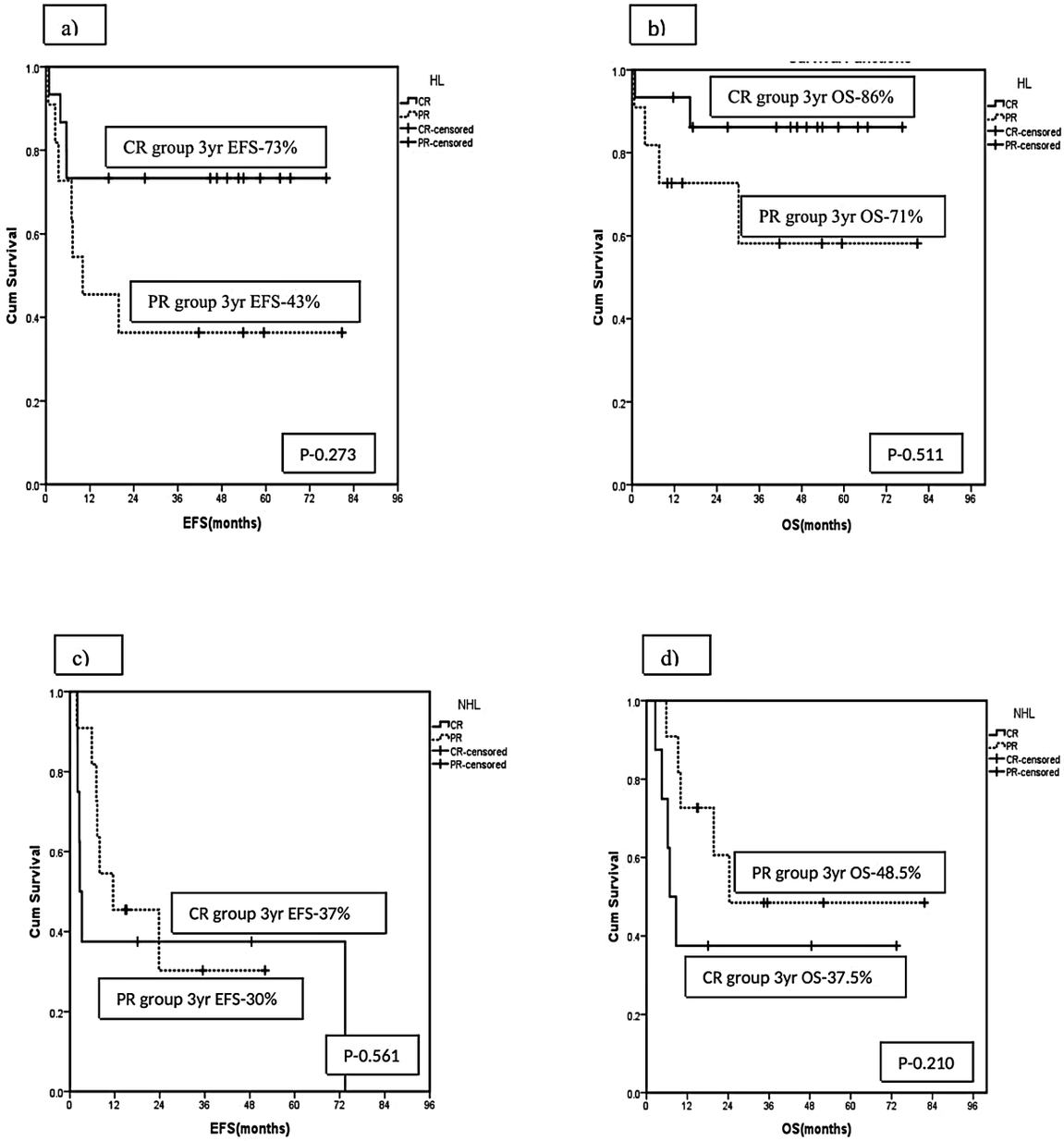

Fig. 2 Kaplan–Meier survival estimate for (A) event-free survival, (B) overall survival for Hodgkin lymphoma, and (C) event-free survival (D) overall survival for non-Hodgkin lymphoma, comparing outcomes with respect to pre-transplant disease status.

The median time to engraftment was 11 days (range: 9–23) and 13 days (range: 8–36) for neutrophils and platelets, respectively. Engraftment time was comparable to results reported with CBV conditioning and other conditioning regimens.[12,13,15,24] Post day 0 (stem cell infusion) hospitalization was for 18 days (range: 10–37) in our study, while it ranged from 17 to 25 days in reports of CBV and other regimens from different transplant settings.[10,11,13,15] During the first 30 days of transplant, PRBC (packed red blood cell) and single donor platelet (SDP) were required for a median of 3 and 4 units, respectively. TPN was used in 7% of our patients, mostly for moderate to severe mucositis, comparable to published data on TPN use for moderate to severe mucositis during lymphoma ASCT.[10,13–15] TRM at 100 days was 6.6% in our cohort comparable to that reported for CBV (7–10%) in other settings.[10,11] A relatively higher TRM (13–18%) has been reported for other conditioning regimens as BEAM.[13,15] Overall, from different studies in the literature, as summarized in ►**Table 3**, including ours, CBV has shown a lower incidence of mucositis and other toxicities, lesser requirement for parenteral nutrition, shorter hospital stay, and lower TRM compared to other conventional regimens.

In our study, post-transplant evaluation of response had shown a CR of 62% and a PR of 20% compared to 49% and 47%, respectively, during the pre-transplant assessment. Thus, about 18% of patients had a progression within 3 months

Table 3 Summary of comparative studies of conditioning regimens for toxicity and survival outcomes in lymphoma

Study	Regimen	Toxicity	TRM (d100-150)	PFS	OS
Arranz et al 1997, Spain[11] HL ($n=49$) Retrospective study	CBV^{high} vs. CBV^{low}	Not reported	9% vs. 8%	47% vs. 29% ($p=0.57$)	Not reported
Salar et al, 2001, Spain[3] NHL ($n=395$) Retrospective study	CBV vs. BEAM vs. CyTBI	Not reported	Not reported	CBV vs. BEAM Relative risk 1.26 (0.77–2.05) ($p=0.34$)	CBV vs. BEAM Relative risk 1.30 (0.74–2.28) ($p=0.36$)
Puig et al, 2005, Spain[12] ($n=113$) NHL($n=69$) HL ($n=44$) Retrospective study	CBV^{high} vs. BEAM	Mucositis (grade 1–2) 6% vs. 34% Pulmonary (grade 3) 4% vs. 0% SOS: 5% vs. 0%	24% vs. 5%	Not reported	Not reported
Harris et al, COG A5962, 2011, USA[16] HL ($n=28$) NHL ($n=10$) Prospective study	CBV single arm study CBV^{high}:450mg/m2 CBV^{low}:300mg/m2	CBV^{high} vs. CBV^{low} Pulmonary toxicity (grade 3/4) 100% vs. 0%	Not reported	3year EFS HL:45% NHL:30%	3year OS HL:63% NHL:34%
Sharma et al, 2013 , India[15] ($n=51$) NHL ($n=26$) HL ($n=25$) Retrospective study	BEAM vs. LEAM	Mucositis (grade 3/4) 68% vs. 65% Diarrhea (grade 3/4) 47% vs. 41%	18% vs. 12%	2 year EFS (HL + NHL) 44.6% vs. 41.1% ($p=0.510$)	2 year OS (HL + NHL) 61.7% vs. 62.7% ($p=0.928$)
Chen et al, 2015, Multicenter study[10] ($n=4,917$) NHL ($n=3,905$) HL ($n=1,012$) Retrospective study	CBV^{high} vs. CBV^{low} vs. BEAM vs. BuCy vs. TBI	CBV^{high} vs. CBV^{low} vs. BEAM Overall toxicity (grade 3–4) 6% vs. 3% vs. 3%	Not reported	CBV^{high} vs. CBV^{low} vs. BEAM 3 year PFS HL 57% vs. 60% vs. 62% DLBCL 39% vs. 47% vs. 47%	CBV^{high} vs. CBV^{low} vs. BEAM 3 year OS HL 68% vs. 73% vs. 78% DLBCL 43% vs. 55% vs. 58%
Khattry et al 2016, India[13] ($N=139$) NHL = 92 HL = 47 Retrospective study	LACE vs. BEAM	Mucositis (grade 3–4) 8% vs. 38%	9% vs. 13%	5-year PFS HL: 39% vs. 48% ($p=0.747$) NHL: 34% vs. 46% ($p=0.709$)	5-year OS HL: 49% vs. 48% $p=0.279$ NHL 37% vs. 46% ($p=0.709$)
SHI et al 2016, China[14] NHL ($n=129$) Retrospective study	CBV vs. BEAM vs. BEAC	CBV vs. BEAM Diarrhea($\geq$ grade 2) 18.8% vs. 63.9% Mucositis ($\geq$grade 2) 25% vs. 47.2%	0%	CBV vs. BEAM vs. BEAC 5-year EFS 43.8% vs. 66.7% vs. 67.5% ($p=0.40$)	CBV vs. BEAM vs. BEAC 5-year OS 68.8% vs. 77.8% vs. 81.8% ($p=0.584$).
Our study ($N=45$) HL = 26 NHL = 19 Retrospective study	CBV–single arm	Diarrhea (grade 3/4) 10% Mucositis (grade 3/4) 9%	6.6%	3-year EFS HL 57.4% NHL 33.7%	3-year OS HL 74.6% NHL 43.4%

Abbreviations: BEAC, BCNU, etoposide, cytarabine and cyclophosphamide; BEAM, BCNU, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, BCNU and etoposide; DLBCL, diffuse large B cell lymphoma; HL, Hodgkin lymphoma; LACE, lomustine, etoposide, cytarabine, and cyclophosphamide; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation; TRM, treatment-related mortality.

of transplant, indicating a high-risk subset who had progressed despite having a chemosensitive disease. There is scant literature on the evaluation of disease response in the immediate post-transplant period as the majority of the studies on autologous transplant in lymphoma describe efficacy outcomes in terms of DFS and OS. Nevertheless, besides chemosensitivity of the disease pre-transplant, other risk factors for progression need further evaluation in a larger cohort.

The median EFS in our cohort was 23.8 months, and the median OS was not reached. As shown in ►**Table 3**, our outcomes were comparable to those reported in the literature for CBV and other regimens for HL and NHL transplants. We observed that patients who had received more than two lines of salvage treatment and patients in PR before transplant had inferior EFS and OS although statistically not significant. In the subset of HL, patients having CR pre-transplant had higher 3-year EFS and OS (73% and 86%, respectively) than patients in PR (43% EFS and 71% OS) although statistically not significant. In the NHL subset, no statistically significant difference was seen in 3-year EFS or OS for patients having CR (37% and 37.5%, respectively) or PR

(30% and 48.5%, respectively) pre-transplant. In several studies in the literature, CR pre-transplant has been shown to be a predictor for better EFS, DFS, and OS in both HL and NHL.[25,26] We did not find any significant difference between patients in CR or PR, possibly due to the small sample size and short follow-up.

Our results and a review of the literature suggest that CBV (low) is generally a safe conditioning regimen with lower toxicities and similar efficacy compared to other conventional regimens, viz. BEAM, BEAC, LACE, or LEAM, especially for patients with HL. However, prospective randomized studies are needed with a larger cohort of patients to know the difference in toxicities and outcomes with various conditioning regimens for lymphoma. Our analysis had limitations inherent to a retrospective study. We had a small number of patients and short follow-up, which precluded any meaningful interpretation of the factors affecting the outcome. Nevertheless, this is the first study from India to report the toxicity profile and efficacy of CBV conditioning.

Conclusion

CBV (low) is relatively safe, with common toxicities being mucositis, diarrhea, CINV, and overall grade 3/4 toxicities experienced by less than 10% of patients. Thus, CBV can be a preferred regimen in resource-limited settings. Event-free survival and overall survival with CBV were comparable to that reported in the literature, especially for patients with Hodgkin lymphoma.

Authors' Contributions

Study conceptualization and methodology: SK, NK, BP, DK, CK, and BD. Data collection and analysis: NK, SK, BP, DK, CK, KR, and MR. Manuscript writing: NK, BP, SK, and PG. Review and editing: SK, BD, and PG. Final approval of manuscript: all authors.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We acknowledge the contribution of JIPMER (Jawaharlal Institute of Postgraduate Medical Education and Research) for providing logistic support for this work. We also recognize the contribution of all the staff and residents of the BMT unit toward dedicated patient care and maintenance of clinical records.

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Mental Wellbeing among Children with Cancer during COVID-19 Pandemic in Indonesia: A Cross-sectional Study

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Ind J Med Paediatr Oncol 2025;46:40–48.

Abstract

Introduction Coronavirus disease 2019 (COVID-19) has affected both physical and mental aspect of people worldwide, especially the high-risk group such as pediatric cancer patients. Children with cancer were considered both clinically and mentally vulnerable during this pandemic. They were also affected by the self-isolation, quarantine, and social distancing policy taken as a respond to public threat.

Objectives To evaluate the impact of social distancing and health protocol during COVID-19 on the mental health profile of children with cancer in Indonesia.

Materials and Methods A cross-sectional study evaluating the mental health of children with cancer during COVID-19 pandemic was conducted in Cipto Mangunkusumo Hospital, Jakarta, Indonesia from June to September 2020. An online questionnaire was used to collect demographics of parents and children, children's Strength and Difficulties Questionnaire (SDQ) score, and parents' Self-Reporting Questionnaire (SRQ). SDQ score consists of five subscales, including the emotional symptoms, conduct problems, hyperactivity, peer relationships problems and prosocial behavior. Cancer types were grouped into retinoblastoma, nonretinoblastoma (other solid tumors), and leukemia.

Results There were 156 valid responses, consisting of 42 patients with retinoblastoma, 34 patients with nonretinoblastoma (other solid tumors), and 80 patients with leukemia. Pandemic-related lifestyle changes did not significantly impact emotional or behavioral problems. Children with normal total SDQ (odds ratio [OR]: 473, $p = 0.001$) and emotional scores (OR: 3.19, $p = 0.07$) had parents with normal SRQ scores (<6). Leukemia patients with shorter diagnosis period had worse hyperactivity score ($p = 0.01$). On the contrary, leukemia inpatients had better prosocial scores than outpatients ($p = 0.03$). More bilateral retinoblastoma patients ($p = 0.04$) with longer duration of cancer diagnosis ($p = 0.03$) faced peer problems.

Keywords
- mental health
- pediatric cancer patients
- COVID-19
- psychiatry
- hematology
- medical oncology
- ophthalmology

article published online
April 28, 2023

DOI https://doi.org/10.1055/s-0043-1768053.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusions Our study revealed that lifestyle changes during early COVID-19 pandemic were not major factors impacting emotional and behavioral problems in children with cancer. However, disease-related factors pose great challenges; thus, a holistic mental health support system should be available to both children and parents.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has posed a global threat since December 2019. It affected both physical and mental health of the public, leading to detrimental effects on quality of life. The World Health Organization expressed concern over the psychosocial consequences of COVID-19, as it stated that the new measures including quarantine and social distancing have disrupted people's routines, thus increasing the feeling of anxiety, depression, loneliness, insomnia, and self-harm.[1–5]

Following government responses to COVID-19 on schools, educational institutions, and closure of public places, ample evidence has revealed the psychological impact of COVID-19 pandemic toward children and adolescents manifesting as behavioral and emotional problems.[6–10] A study showed that children who have more highly educated parents, live in big cities, come from either high- or low-income households, and have parents with mental problems are the most vulnerable group during the pandemic. There is also evidence that extended period of parental stress during the pandemic is related to child behavioral problems.[11]

Children and adolescents faced emotional struggles while experiencing social isolation and disrupted education. Children encountered fear, uncertainties, and isolation, resulting in conditions such as poor appetite, physical discomfort, agitation and inattention, clinginess, separation problems, and poor sleep.[6–10] In published research on stress levels among students during the pandemic, the values ranged from 24.7 to 71.2%, mostly related to the adaptation of long-distance learning.[12–14] In addition, the increased use of digital devices during lockdown has also been used as indicator of developing the internet addiction, gaming disorder, anxiety, depression, irritability, sleep disturbance, and poor mental health in children during the pandemic.[12–15]

Pediatric cancer patients are not indifferent to the dramatic impact of COVID-19. The uncertainty regarding their condition is now worsened by the risk of contracting viral infection and disruption in cancer treatment protocol.[16,17] Even before the pandemic, children with cancer were already at risk of developing mental health disorders precipitated by the anxieties following diagnosis, treatment, and alteration of daily activities. The side effects of cancer treatments, including surgery, chemotherapy, and radiotherapy, may lead to cognitive problems, behavioral disorders, and poor coping skills. There are also increased levels of depression, anxiety, and concerns related to mortality.[18–20]

Children with cancer are considered as clinically vulnerable during this pandemic due to their immunocompromised status caused by cancer and anticancer treatments.[17,20,21] Hence, they are recommended to undergo stricter rules to keep them safe by always remaining at home and avoiding contact with anyone beyond their household, except attending medical care in the hospital. There is an emerging concern regarding the damage of these measures on the mental wellbeing of pediatric cancer patients.[16,22–25] A study in Milan showed that majority of adolescent cancer patients were worried and felt personally at risk during this pandemic, as they encountered high levels of stress and anxiety, facing dilemmas regarding continuation of their treatment and access to health care facility under these threatening circumstances.[17,22–26]

Not only the patients but also the families of children with cancer experience challenges in balancing their life during the pandemic. A study in UK found that parents/caregivers were worried that their children would get infected by the virus and felt that hospital was not a safe place, thus increasing parents' anxiety and concerns about their child's care.[26,27] Another study also stated that hospital restriction increased parent's psychosocial distress during the pandemic, especially regarding the risk of suboptimal care received by their children.[27–29]

There are limited data on the mental health status of pediatric patients with cancer during the COVID-19 pandemic. Therefore, we conducted the first Indonesian study that aimed to evaluate the experience and psychological impact of COVID-19 toward children with cancer and their parents in Indonesia. These findings can provide comprehensive foundation for the development of mental health programs to support children with cancer during this pandemic.

Materials and Methods

Study Design and Data Collection

A cross-sectional survey study of parents and children with cancer diagnosed between 2015 and 2020 was conducted to assess their mental health and experience during the social isolation of COVID-19 pandemic. The data were collected by clinicians who are members of the research team (R. M., A. S. N., N. S.) from June to September 2020, 3 months after the start of social distancing and lockdown implementation in Indonesia.

The variables in our study are as follows: gender, age, education level, parent's marital status, time from diagnosis to data collection (TDD), treatment status, place of stay during self-isolation, duration of study from home per day, total duration of using gadget per day, cancer staging, treatment received, phase of treatment, number of eyes affected (retinoblastoma patients), children's Strength and

Difficulties Questionnaire (SDQ) score, emotional problems score, conduct problems score, hyperactivity score, peer problems score, prosocial score, and parents' Self-Reporting Questionnaire (SRQ) score. The primary outcomes of this study are the association between patient's clinical characteristics (cancer staging, types of treatment, and TDD) and their total SDQ score (and its domain) during the COVID-19 self-isolation period. The secondary outcomes are the patients' and their parents' demographic characteristics (gender, age, total screen time, treatment status, place of stay during pandemic, marital status, parents' marital status, and parent's SRQ score) and their association with the SDQ score (and its domain), in addition to the comparison between each cancer group.

The inclusion criteria of this study were parents and their children aged between 0 and 18 years, who were clinically diagnosed with cancer (either were still undergoing treatment or had completed their treatment) and were literate and able to respond to questions in Indonesian language. Patients were recruited from Pediatric Oncology and/or Pediatric Ophthalmology Department outpatient clinics, Ciptomangunkusumo Hospital. We exclude parents and children who refused to complete the questionnaire or are not able to comprehend and respond to questions.

Instrument

We gathered information on parents' and children's demographics and then evaluated their experiences during the COVID-19 pandemic including the social distancing practice, work/study from home practice, problems, and hopes during this pandemic. A questionnaire was developed to address the lifestyle-related behavior changes during the pandemic including the duration of work from home and study from home, source of COVID-19 information, and problems experienced during the pandemic.

The main outcome, which is the mental condition of the pediatric cancer patients, was assessed using validated questionnaire. The survey was conducted via an online survey tool (Google Forms) in Indonesian language, available in the ►**Appendix 1**. Before we performed the statistical analyses, all patient-related medical information was validated through the medical record.

SDQ for Children

The emotional and behavioral problems of the children were assessed using the SDQ.[30,31] The SDQ questionnaire was each categorized based on the age of the children, which consists of a parent-completed SDQ for ages 2 to 4 years old[30] and 4 to 11 years old,[31] and a self-completed SDQ for ages 11 to 18 years old. SDQ had been officially translated and validated into Indonesian language by one of our authors (T. W.). It is available as online assessment tool for children at www.sdqinfo.com. SDQ for ages 11 to 18 years was filled in by the children themselves, meanwhile SDQ for ages 2 to 11 years was filled in by their parents.[30,31]

The SDQ questionnaire consists of 25 questions on Likert scale (0 = not true; 1 = somewhat true; 2 = certainly true). It was divided into two major parts including the difficulties domains, which consist of 20 questions (emotional problems, conduct problems, hyperactivity scale, and peer problems), and strength domain, which comprises 5 questions (prosocial scale). The total score for the difficulties domains ranged from 0 to 40. The newer four-band categorization was used as cutoff points for total SDQ score and its domain in our study. The initial three-band categorization divided SDQ scores as "normal," "borderline," and "abnormal," with cutoff points such that 80% of children population scored "normal," 10% "borderline," and 10% "abnormal." New four-band classification with cutoff points such that 80% of children population were "close to average," 10% "slightly raised," 5% "high," and 5% "very high" for all scales except prosocial, which is 80% "close to average," 10% "slightly lowered," 5% "low," and 5% "very low," was used.[30,31]

SRQ for Parents

Parents also completed the SRQ consisting of 20 yes/no questions, which has been translated and validated in Indonesian language, with a cutoff score of 6 to be indicative of common mental disorder.[32]

Definitions

TDD was defined as the duration of time since the patient was diagnosed with cancer until the data were obtained. We classified patients into three groups: retinoblastoma, leukemia, and nonretinoblastoma (other solid tumors) group. We defined combined therapy in both retinoblastoma and nonretinoblastoma (other solid tumors) groups as combination of surgical, chemotherapy, radiotherapy, and other modalities. Monotherapy in the nonretinoblastoma (other solid tumors) group was defined as surgical only or chemotherapy only. The retinoblastoma group was classified into early (stage 1 and 2) and advanced (stage 3 and 4). Cancer staging in nonretinoblastoma (other solid tumors) diagnosis was grouped into early to advanced (stages 1, 2, and 3) and late (stage 4). The treatment phase in leukemia group was categorized into two groups based on the treatment received, namely, inpatient, which consists of induction, consolidation, and intensification phase, and outpatient, which consists of maintenance and remission phase.

Statistical Analyses

From questionnaire results, we excluded housewives and unemployed in the analysis of "work from home" variable. We also excluded patients who received chemotherapy only in the retinoblastoma group from the analysis of "treatment received for cancer" as they have not completed treatment regimen.

Statistical analysis was performed with SPSS version 24.0 for Mac (SPSS Inc., Chicago, IL, United States). Categorical data were reported in the form of frequency (percentage) and assessed using chi-square (χ^2) test or Fisher's exact test. Continuous variables were reported in the form of mean ± standard deviation or median (range). Normality of the data was evaluated by using Shapiro–Wilk test. Normally distributed data were analyzed using one-way analysis of variance. Nonnormally distributed data were analyzed using Kruskal–Wallis test.

Analysis was conducted according to the cancer diagnosis, grouped as retinoblastoma, nonretinoblastoma (other solid tumors), and leukemia. Descriptive statistics were carried out to summarize all variables included based on the diagnosis groups. We performed a bivariate analysis and risk assessment on parents' and children's characteristics toward children's SDQ score. A p-value < 0.05 was considered statistically significant.

Ethics

This study has been approved by the Research Ethic Committee in Cipto Mangunkusumo Hospital, Jakarta (KET-476/UN2.F1/ETIK/ PPM.00.02/2020), as listed in ►**Appendix 2** and conducted in accordance with the tenets of the Declaration of Helsinki. All participants were provided study information and completed electronic consent before completing the online survey.

Results

Patient's Clinical Characteristics

A total of 166 patients were assessed for enrollment. Ten patients were excluded and 156 patients who met the eligible criteria were included in the study, as seen in ►**Fig. 1**. Among them, 42 patients belonged to the retinoblastoma group, 34 patients were in the nonretinoblastoma (other solid tumors) group, and 80 patients were diagnosed with leukemia. Half of our retinoblastoma patients suffered from unilateral cases (50%, $n = 21$). Approximately 85.7% ($n = 36$) of the children were in the early stage (stages 1 and 2) of the disease. The combination of enucleation and chemotherapy was the most common treatment modality given in accordance with disease stage. Meanwhile, the diagnosis for the other (nonretinoblastoma) solid tumor group in our study included neuroblastoma (26.5%, $n = 9$), lymphoma (23.53%, $n = 8$), rhabdomyosarcoma (11.76%, $n = 4$), osteosarcoma (11.76%, $n = 4$), and others (26.47%, $n = 9$). Around 70.58% ($n = 24$) came to the hospital during late stage of the disease (stages 3 and 4). The most common types of treatment given to these patients were chemotherapy only (41.2%, $n = 14$) and combination of chemotherapy and surgery (23.5%, $n = 8$). Lastly, 75.75% ($n = 59$) of leukemia patients in our study were in maintenance phase of chemotherapy treatment. Patient's demographic characteristics are listed in ►**Table 1**. Patients' clinical information based on the cancer diagnosis is summarized in ►**Table 2**.

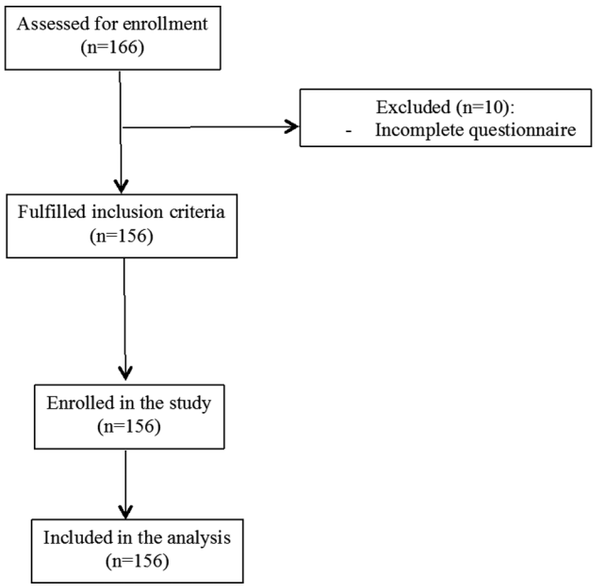

Fig. 1 Consort diagram showing participants enrollment.

Patients' Clinical Data and SDQ Score

►**Appendix 3** displayed comparison between total SDQ score and its domains based on clinical characteristics in each cancer group. Our results showed significant differences in the scores of three domains, including hyperactivity, peer problems, and prosocial domains between cancer groups. Significantly shorter TDD in leukemia patients was found in group with at-risk hyperactivity score ($p = 0.01$). Numbers of bilateral retinoblastoma patients ($p = 0.04$) and patients who were diagnosed longer ($p = 0.03$) were also significantly higher in group with at-risk peer problems score. Lastly, the prosocial score of the leukemia group was significantly different between those receiving inpatient and outpatient treatments ($p = 0.03$).

Parents'/Children's Demographic Characteristics and Children's SDQ Score

The comparison between total SDQ score and its domain based on parents' and children's demographic characteristics is detailed in ►**Appendix 4**. Several characteristics should be highlighted. Children with normal total SDQ (odds ratio [OR]: 473; 95% confidence interval [CI]: 45.04–4,975.42; $p = 0.001$) and emotional problems (OR: 3.19; 95% CI: 0.91–11.18; $p = 0.07$) scores had parents with normal SRQ score (<6) during this COVID-19 pandemic. A significant difference was also seen in the emotional problems, conduct problems, and prosocial scores among the children's age groups. Compared with children aged 10 to 17 years, preschool children aged between 0 and 5 were more likely to experience problems in emotional (OR: 4.83; 95% CI: 1.36–17.11; $p = 0.02$) and prosocial scores (OR: 3.27; 95% CI: 1.31–8.19; $p = 0.01$), while children aged 6 to 9 were more likely to face emotional (OR: 5.07; 95% CI: 1.21–21.23; $p = 0.03$) and conduct problems (OR: 8.19; 95% CI: 2.02–33.19; $p = 0.003$). In addition, most of the children with emotional problems also were still on their cancer treatment during the survey rather than being cancer survivors (OR: 2.11; 95% CI: 0.92–4.83; $p = 0.07$).

Comparison of Children's SDQ Score among the Cancer Diagnosis Groups

The comparison of children's SDQ score and its domain between the diagnosis groups showed no significant difference of children's SDQ score and its domain between the three diagnosis groups.

Discussion

Children with cancer face stress not only from their medical condition but also from lifestyle changes brought about by

Table 1 Children's demographic characteristics based on cancer diagnosis

	Retinoblastoma ($n = 42$)	Solid tumor (nonretinoblastoma) ($n = 34$)	Leukemia ($n = 80$)
Gender			
Male	26 (61.9%)	20 (58.8%)	47 (58.8%)
Female	16 (38.1%)	14 (41.2%)	33 (41.3%)
Age (y)	4 (1–11)	5 (1–17)	6 (1–16)
0–5	33 (78.6%)	20 (58.8%)	34 (42.5%)
6–9	8 (19%)	3 (8.8%)	17 (21.3%)
10–17	1 (2.4%)	11 (32.4%)	29 (36.2%)
Education level			
Preschool	29 (69%)	19 (55.9%)	30 (37.5%)
Kindergarten	7 (16.7%)	2 (5.9%)	9 (11.3%)
Elementary school	6 (14.3%)	4 (11.8%)	25 (31.3%)
Junior high school	0 (0%)	8 (23.5%)	9 (11.3%)
Senior high school	0 (0%)	1 (2.9%)	6 (7.5%)
University	0 (0%)	0 (0%)	1 (1.3%)
Time from diagnosis to data collection (mo)	24 (1–96)	12 (3–48)	17.5 (1–72)
Treatment status			
On treatment	15 (35.7%)	30 (88.2%)	75 (93.8%)
Survivor	27 (64.3%)	4 (11.8%)	5 (6.3%)
Place of stay			
Private housing	16 (38.09%)	9 (26.47%)	40 (50%)
Temporary housing	26 (61.91%)	25 (73.53%)	40 (50%)
Duration of study from home per day (min)	0 (0–120)	0 (0–240)	45 (0–300)
Total duration of using gadget per day (min)	60 (0–540)	80 (0–540)	120 (0–780)

pandemic. Their ability to cope with additional stress is a cause of concern as psychological and social problems could affect the children's enthusiasm in continuing cancer treatment and their ability to adapt to new lifestyles. Recommendation regarding standard of care in children with cancer provides insight to balance the risk of COVID-19 and continuation of care for children, which caused burden and challenges toward parents, children, and health care providers.[16] A study in UK reported an increased worry experienced by parents of a child with cancer.[26] In addition, children with cancer and their families also expressed their concerns living in a life of uncertainty, which leads to fear of adaptation, loneliness, and confusion.[17] Our study showed that pandemic-related changes such as increased screen time, place of stay during lockdown, and duration of homeschooling did not significantly affect their psychosocial wellbeing. Disease-related factors such as TDD, being on treatment, and other factors such as gender, age, and parental SRQ scores had greater influence instead.

Lifestyle Changes during the Pandemic

To our surprise, in our study lifestyle changes during the COVID-19 pandemic were not significant factors in determining social and psychological problems in children with cancer. This was supported by other studies as well. A Dutch study[26] had also reported that there was no significant difference in psychosocial health of children with cancer before and during the pandemic. Children with chronic illness and cystic fibrosis who were thought to have risks of developing psychosocial problems during the pandemic were also not significantly affected.[33,34]

In addition, more than half of our patients (58.3%) undergoing treatment lived in temporary housing such as rentals and boarding home for childhood cancer patients. The boarding home for childhood cancer patients helped establish a community of patients and their guardians for mutual support. Hence, this could be a possible explanation why the place of stay did not have a significant impact on the psychosocial health of the patients.

The Impact of Increased Screen Time

School closures, homeschooling that utilized online learning, lockdown, and isolation resulted in a sharp increase of screen time for children. Children in our study experienced a median of 160 minutes of daily screen time. Our data revealed that total screen time per day did not significantly

Table 2 Clinical characteristics of cancer patients based on the diagnosis

Retinoblastoma patients ($n = 42$)	
Number of eyes affected	
Unilateral	21 (50%)
Bilateral	21 (50%)
Cancer staging	
1	21 (50%)
2	15 (35.7%)
3	4 (9.5%)
4	1 (2.4%)
Treatment received for cancer	
Enucleation	10 (23.8%)
Enucleation, chemotherapy	22 (52.4%)
Enucleation, chemotherapy, laser	6 (14.3%)
Enucleation, chemotherapy, radiation	2 (4.8%)
Chemotherapy	2 (4.8%)
Other solid tumor (nonretinoblastoma) patients ($n = 34$)	
Diagnosis	
Neuroblastoma	9 (26.47%)
Lymphoma	8 (23.53%)
Rhabdomyosarcoma	4 (11.76%)
Osteosarcoma	4 (11.76%)
Others	9 (26.47%)
Cancer staging	
1	1 (2.94%)
2	9 (26.47%)
3	12 (35.29%)
4	12 (35.29%)
Treatment received for cancer	
Chemotherapy	14 (41.2%)
Chemotherapy, operation	8 (23.5%)
Chemotherapy, radiation	5 (14.7%)
Chemotherapy, operation, radiation	3 (8.82%)
Operation	4 (11.76%)
Leukemia patients ($n = 80$)	
Phase of treatment	
Induction	3 (3.75%)
Consolidation	11 (13.75%)
Intensification	2 (2.5%)
Maintenance	59 (73.75%)
Remission	5 (6.25%)
Treatment received for cancer	
Chemotherapy	80 (100%)

impact children's mental health during the pandemic. This was different from previous findings,[32,35,36] which showed that excessive screen time was related to poorer mental health. Another study[29,37] had also shown that these detrimental effects were related to social media and Internet use, but not gaming and watching television.

The necessity of gadget usage during the pandemic for schooling and entertainment activities for children staying at home could help them cope with stress instead. This solution may be helpful in the short term, but can turn out to be inappropriate or even bad in the long run. Recreational screen use may be good for children, to a certain extent, during this difficult pandemic. It is also important to inform parents about the importance of controlling their child's screen time and content. Therefore, parents should establish sufficient screen-free periods each day.[32,36,37]

Mental Wellbeing in Retinoblastoma Patients

Disability brought about by pediatric cancer can be detrimental to children's mental wellbeing. Our study showed that children with bilateral retinoblastoma faced difficulties with peers, which could be linked to their loss of sight. Longer duration since cancer diagnosis also significantly raised the risk of peer problems. Retinoblastoma patients in developing countries such as Indonesia often exhibit symptoms long before seeking medical help; therefore, the duration is an underestimation of the actual TDD. Retinoblastoma patients often present with advanced stage at diagnosis. As most children with retinoblastoma had to undergo enucleation surgery, visual impairment could cause their peer problems. A recent study in China by Feng et al[38] revealed that retinoblastoma survivors who underwent enucleation were more self-conscious about their appearance resulting in low self-confidence. In our study, visual disability not only reduced self-confidence but also caused problems in socializing with their peers. A study conducted in the Netherlands by van Dijk et al[39] found that 88% of adult retinoblastoma survivors had experienced bullying related to their appearance, eye prosthesis, and their visual impairment and blindness, which consequently affected their mental health. Participants also mentioned that their peers had difficulty reading their facial expressions and emotions due to lack of eye contact. Unlike children with other forms of cancer, children with retinoblastoma face greater challenges as their sight and appearance are adversely affected. Children with cancer and resulting disabilities should receive guidance on dealing with peer problems and psychological counseling when necessary.

Mental Wellbeing in Leukemia Patients

Our study showed that in children with leukemia, outpatients were at higher risk of prosocial problems than inpatients. Outpatient treatment can impose more problems for children with cancer, as they are required to socialize with other children and family members outside of the hospital environment. Lengthy period of previous hospitalization might have affected their prosocial abilities. A Turkish

study[40] of leukemia survivors found that children were unwilling to reattend school after treatment and their parents were more likely to restrict their social activities, as they feared that the children were more vulnerable of infections. Outside the hospital, children should be encouraged to socialize, and adequate guidance should be given to allow them to build friendships with other children.

Leukemia patients in our study with shorter period since diagnosis (median of 5 months) were associated with hyperactivity problems. Patients and parents alike were often in denial after initial diagnosis of leukemia. Furthermore, chemotherapy regimen would be in the induction stage for the initial 4 to 5 months when children would experience strong side effects from intense chemotherapy treatment. At the maintenance stage, however, chemotherapy regimen is less intense, and children are better adjusted to chemotherapy. Children initially diagnosed with cancer exhibit hyperactive behavior to gain more parental care as coping mechanism. In contrast, children with retinoblastoma who experienced peer problems had longer period of cancer diagnosis. Chemotherapy for retinoblastoma does not follow the induction–maintenance regimen but is administered in cycles. Longer period since diagnosis meant that children undergo intense chemotherapy in repetitive cycles and repeatedly affected by side effects.[41,42]

The Psychological Impact of COVID-19 in Younger Children

Across the board, adolescents aged 10 to 17 were less likely to be at risk of emotional problems compared with younger children. A study by Bloom et al[43] also supported this finding, showing that younger children were more negatively affected by lockdown and had more mental health problems than adolescents, including emotional problems, misconduct, and hyperactivity.

Young children aged 0 to 5 showed highest risk of hyperactivity and prosocial score. This was in line with another study, which reported an increased inattention and hyperactivity/impulsivity were seen on young children aged 4 to 6 years during the pandemic.[44] In our study, children aged 6 to 9 were most likely to experience emotional problems and conduct problems. On the other hand, a study in UK reported those aged 7 to 12 years found depression symptoms worsened but reported no significant changes for anxiety symptoms and emotional problems.[6,45,46] A contradictive result was shown in study of pediatric patients with rheumatological diseases, in which female adolescents diagnosed with juvenile idiopathic arthritis experienced more anxiety and depressive symptoms during the pandemic.[47]

Children under 9 years were less able to cope and verbalize their discomfort of their experience; therefore, they express misbehavior and misconduct. It highlights the impact that the COVID-19 pandemic and consequent restrictions might have had on children who are perhaps too young to understand the meaning of the pandemic, compared with adolescents. Younger children are a lot more reliant on their parents throughout the day including support with education and monitoring, entertaining, and providing for them. On the contrary, adolescents may have been more independent during lockdown with better access to their peers.[6,42,46]

Impact of Parents' Mental Health Status toward Children

Parents have a large impact on the mental health of children with cancer. Our analysis showed that parents with SRQ score $\geq$ 6 who were more likely to face psychological problems might affect their children to be at greater risk of facing psychological difficulties. Studies also reported that during COVID-19 pandemic, parents of children with cancer have increased sense of isolation and loneliness, especially due to the lack of support from family, friends, relatives, and cancer support group[17,27] in addition to the high stress level and significant level of anxiety.[48] Several studies[49,50] had shown that parents of children with cancer were psychologically distressed due to mental and financial burden of caregiving. Parents with psychological problems were less able to build healthy parent–child relationships. In comparison to another study in highly vulnerable group of children with rare diseases, a study by Rihm et al also reported a high psychosocial burden in caregivers and reduced quality of life in children with rare diseases.[51] A similar trend was also observed in both caregivers and children with type 1 diabetes.[52]

A study by Kim et al[53] also reported an increased risk of children sleep and behavioral problems related to parents' stress and depression during the pandemic. Reciprocal relationship between parents' and children's mental health was also seen, especially associated with higher levels of depression, anxiety, and stress.[43] Hence, not only should children be provided with psychological support, but also parents should have access to mental health care and make effort to build healthy parent–child relationships.

Our study has several limitations. First, the study population was not enough to draw a generalized conclusion, which represents the whole diagnosis groups in pediatric cancer patients as the study only covered pediatric cancer patients in a single institution using a convenience sampling method. Second, the data collection was conducted through self-report surveys and online questionnaires. We recommended psychiatrists to perform clinical in-depth interview in follow-up studies in order to gain detail regarding factors affecting the mental health conditions of pediatric cancer patients during this pandemic. In addition, the self-report nature of the assessment tools used in our study also increases the chance of subjectivity of the answers. Third, several important factors that may affect the outcome such as friends and families support, information collection regarding COVID-19 and mental health during the pandemic, and coping strategies were not included in the analysis. Therefore, further studies with larger samples and more comprehensive assessment should be conducted in order to gain a better understanding of pediatric cancer patients' mental wellbeing during this COVID-19 pandemic.

Conclusion

Our study has shown that although the pandemic has altered the routine and lifestyles of children with cancer, disease-

related factors had greater impact on their mental health. Children with cancer might even benefit from more time spent at home and increased interaction with parents working from home. The process of cancer treatment and having less developed emotional coping ability pose risks to their emotional and behavioral wellbeing. These findings highlight the ongoing need to target vulnerable groups. A holistic mental health support system is essential for both children and parents to help them promote self-management, enhance physical and psychological wellbeing, and raise their quality of life.

Authors' Contributions

R. S. S., T. T. S., T. W., S. D. E., and I. S. W. designed and conceptualized the study. R. M., A. S. N., and N. S. carried out the survey. R. S. S., T. T. S., T. W., S. D. E., I. S. W., N. S., and S. T. analyzed the data and wrote and edited the manuscript. All authors have read and approved this manuscript.

Funding

None.

Conflict of Interest

None declared.

Acknowledgements

The authors would like to acknowledge Mrs. Ira Soelistyo, Chairperson of Indonesia Care for Cancer Kids Foundation (Yayasan Kasih Anak Kanker Indonesia) for aiding us in distributing online questionnaire for this study.

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Assessment of Cancer Chemotherapy Needs in Patients Attending Tertiary Care Cancer Center, q: A Cross-Sectional Study

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Ind J Med Paediatr Oncol 2025;46:49–56.

Abstract

Introduction Globally, 19.3 million new cancer cases were diagnosed in 2020, with over 10.0 million cancer deaths. Patients with cancer often face various long-term physical, social, financial, psychological, and existential challenges, complicating their survivorship.

Objectives This study aimed to evaluate the different needs of patients undergoing chemotherapy at a tertiary care cancer center.

Materials and Methods Data were collected from a tertiary care cancer center using purposive sampling. A total of 101 samples were collected over a 2-month period.

Results The majority of participants were female (61.4%), with 38.6% being male. Most participants were in the third stage of cancer (57.4%), with 42.6% in the fourth stage. Localized metastasis was observed in 83.2% of participants. The most common symptoms were lack of appetite (59.4%) and nausea/vomiting (54.5%). Most participants rated the care provided by nurses during chemotherapy as good (86.1%). The majority had moderate needs (67.3%) during the treatment course.

Conclusion The study highlights significant needs in the physical and psychological domains among patients undergoing chemotherapy.

Keywords
- cancer needs assessment
- chemotherapy
- physical needs
- psychological needs

Introduction

Cancer is a major disorder that causes millions of deaths worldwide. Cancer cells divide uncontrollably, leading to tumor growth and immune system dysfunction. Due to factors such as population ageing, tobacco use, radiation exposure, adopting a more sedentary lifestyle, and genetic predisposition, its incidence has increased in recent years.[1] Globally, 19.3 million new cancer cases have been diagnosed in 2020, with over 10.0 million cancer deaths.[2]

According to recently released cancer facts and figures reported by the International Agency for Research on Cancer, there has been an overall increase in the cancer burden in South Asia over the last decade. The region is now home to almost a quarter of new cancer cases globally and is also expected to have the highest growth rate among all other regions by 2030.[3] Cancer remains a largely dreaded illness and is usually associated with death, but this may not always be true. Although it is still one of the top three leading causes

article published online
July 18, 2024

DOI https://doi.org/10.1055/s-0044-1787149.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of death in India and several other developing countries, it can be managed if diagnosed early.[4]

The increase in cancer burden in India can be attributed to several factors, such as an ageing population, an unhealthy lifestyle, and an increase in obesity. While the proportion of people with cancers in older age groups is expected to increase, the proportion of people younger than 50 with cancer is also expected to increase. Certain risk factors for cancer, such as tobacco use, unhealthy diet, and alcohol consumption, are expected to increase, contributing to the country's increased cancer burden.[5]

As a result of the current advances in cancer treatment and the evolving landscape of clinical trials, more adults are surviving cancer and living longer than ever before. The most common cause of cancer death is lung cancer, with 1.8 million deaths predicted.[6]

Patients with cancer may experience varying degrees of long-term physical, social, financial, psychological, and existential distress, complicating their survivorship. Cancer survivors may experience physical and psychological symptoms beyond 10 years after treatment completion, even though some cancer-related concerns usually decrease over time. These symptoms may include fatigue, pain, and sleep difficulty.[7]

Despite providing chemotherapy, many patients experience various symptoms in the form of adverse effects, a major drawback of chemotherapy.[8] The physical domain describes the adverse effects of chemotherapy. Other unmet needs are also present during treatment, crucial for improving quality of life. Psychological factors also play a major role in quantifying the health-related quality of life in cancer patients who may experience different psychological disturbances during the treatment.[9]

In the context of increasing cancer burden and the significant impact of chemotherapy on patients' well-being and quality of life, it is essential to evaluate the specific needs of individuals undergoing this treatment. This study aimed to assess the needs of patients undergoing chemotherapy at a tertiary care cancer center. By understanding these needs, health care providers can address chemotherapy-related adverse effects and improve patient-centered care. The findings of this study will inform clinical practice, guide future research, and contribute to interventions that optimize the chemotherapy experience of patients. The main objectives of the study were to assess the needs of patients undergoing chemotherapy for cancer and determine factors associated with these needs.

Methodology

This study used a cross-sectional design to assess the different needs of cancer chemotherapy patients in a tertiary care cancer center. Data collection was conducted over 2 months using purposive sampling. The sample size of 101 participants was calculated based on a 2% prevalence of cancer in the Mysuru district, Karnataka, India, with an absolute precision of 2.8% and a confidence interval of 95%. Patients who provided informed consent and were free of psychological disorders were included. Those in terminal cancer stages were also included to capture a full range of experiences. Data was collected over 2 months through interviews using the validated Cancer Needs Assessment Tool-Chemotherapy (CNAT-CC) questionnaire.[10] The CNAT-CC has defined cutoff scores to classify needs as no need (0–25), moderate need (26–50), and high need (51–75).

The term "need" refers to cancer chemotherapy patients' perceived or identified requirements, demands, or necessities. These needs encompass various aspects such as physical symptoms, psychological well-being, information, support, and other elements essential for the comprehensive care and well-being of individuals receiving chemotherapy.

Data was entered in Microsoft Excel 2019 and analyzed using SPSS version 26 (licensed to the institution). Data analysis involved descriptive statistics in determining the frequency and percentage of different needs, and the chi-square test was used to explore the associations between dependent and independent variables. This study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. All procedures involving human participants were conducted following the guidelines of the Institutional Ethical Committee. The study was approved by the Institutional Ethical Committee (approval number: JSSMC/IEC/03072023). Informed consent was obtained from each participant before the commencement of the study.

Results

Data were collected from 101 participants. The majority of the participants in the current study were females (61.4%), and 38.6% were men. Most participants in the current study belonged to the Hindu religion (92.1%), while 4% belonged to Muslims and Christianity. From the current study participants, 54.5% belonged to rural areas, whereas 45.5% were from urban areas. Most participants in the current study were illiterate (33.7%), and 12.9% had a diploma or degree.

Most of the participants in the current study were semi-skilled (33.7%), and the least were unskilled (13.9%). The majority of the participants belonged to socioeconomic class II; that is, their income lies between 3,504 and 7,007 INR, and the least (5%) belonged to socioeconomic class V (1,050 INR and below). Most of the participants in the current study had joint families (49.5%), followed by nuclear families (42.6%) and three-generation families (7.9%).

Personal History and Disease Profiles

Most participants in the current study were in third stage of cancer (57.4%), and 42.6% were in fourth stage. Localized metastasis was observed in 83.2% ($n = 84$) of the participants. This indicates that cancer had metastasized locally from the original tumor to nearby lymph nodes or tissues for these patients but had not spread further to distant sites in the body. Regional tumors refer to cancer that has spread outside the original site to nearby organs, lymph nodes, or tissues. In this study, 4% ($n = 4$) of participants had regional tumors, meaning their cancer had spread regionally from the

primary site to adjacent organs or structures but not yet distantly throughout the body.

Comorbidities were absent in most participants ($n = 85$, 84.2%). Among those with comorbid conditions, diabetes was present in 3% ($n = 3$), diabetes with cardiovascular disease in 3% ($n = 3$), diabetes with hypertension in 5.9% ($n = 6$), and hypertension alone in 4% ($n = 4$). The majority of participants were undergoing chemotherapy (66.3%), followed by surgery + chemotherapy (14.9%), and triple therapy (surgery + chemotherapy + radiation) (12.9%). Note that 33.7 had lung cancer and 17.8% had rectal carcinoma, followed by breast carcinoma (12.9%), esophageal carcinoma (10.9%), and carcinoma of the stomach (8.9%). Acute leukemia was present in 5.9% of the participants (►**Table 1**).

Table 1 Clinical profile of the study participants

Personal history		
	n	%
Stage of cancer		
3	58	57.4
4	43	42.6
Type of tumor		
Regional	4	4.0
Localized metastasis	84	83.2
Metastasis	13	12.9
Comorbidities		
DM	3	3.0
DM and CVD	3	3.0
DM and HTN	6	5.9
HTN	4	4.0
Nil	85	84.2
Treatment		
Chemotherapy	67	66.3
Surgery + chemotherapy	15	14.9
Chemotherapy and radiation	6	5.9
Surgery + chemotherapy + radiation	13	12.9
Type of Cancer		
Acute leukemia	6	5.9
Carcinoma of breast	13	12.9
Carcinoma of colon	2	2.0
Carcinoma of esophagus	11	10.9
Carcinoma of leiomyosarcoma	3	3.0
Carcinoma of lung	34	33.7
Carcinoma of ovary	5	5.0
Carcinoma of rectum	18	17.8
Carcinoma of stomach	9	8.9

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.
Note: Values are expressed as frequency and percentages.

Physical Needs

The majority of participants had a lack of appetite (59.4%). Nausea and vomiting sensations were present in 54.5% of participants. Forty-seven percent of the participants felt lethargic and fatigued during chemotherapy cycles.

Hair loss was seen in 60.4% of the participants during the treatment. Most participants (58.4%) had pains/aches during chemotherapy. Breathlessness was observed in a few participants (23.8%) (►**Fig. 1**).

Psychological Domain

Regarding psychological symptoms, 33.7% of the participants had anxiety and 9.9% felt depressed. Some participants stated they felt stressed during chemotherapy (19.8%) and 11.9% felt lonely.

Of the participants, 27.7% said they feared chemotherapy sessions and 12.9% said they feared hospitalization (►**Table 2**).

Hospital Care Domain

Most participants reported that their care needs were adequately met, with 86.1% ($n = 87$) stating that nurses provided good care during chemotherapy. Most participants (87.1%, $n = 88$) indicated their communication needs with doctors were well met. Prompt treatment for adverse reactions was received by most participants (88.1%, $n = 89$), meeting their needs for timely management of chemotherapy side effects. Most participants (92.1%, $n = 93$) reported that their needs for satisfactory care from treating doctors were fulfilled. The need for doctor availability in an emergency was met for 91.1% ($n = 92$) of participants. Most participants (89.1%, $n = 90$) had their needs met to be involved in treatment decisions, indicating their self-determined needs were satisfied. The hospital care domain reflects that most participants had their essential care and communication needs met during chemotherapy.

Information and Communication Domains

Moderate need (20.8%) was available for patients regarding the information provided regarding chemotherapy.

A moderate need (77.2%) was observed regarding information on adverse drug reactions and their occurrence during chemotherapy.

Information regarding emergencies (21.8) and self-management of drug reactions is in moderate need (24.8%).

Five percent of the participants felt they needed information on financial schemes by the government or private agencies. Participants stated that they had a moderate need for information on the current state of illness (15.8%), contact details of the treating physician (9.9%), and total expenditure on chemotherapy (26.7%).

Practical Needs Domain

Among the participants, 19.8% reported needing family support during chemotherapy. Most participants needed financial support (43.6%).

Note that 35.6% of the participants stated they needed transportation services to attend the chemotherapy sessions.

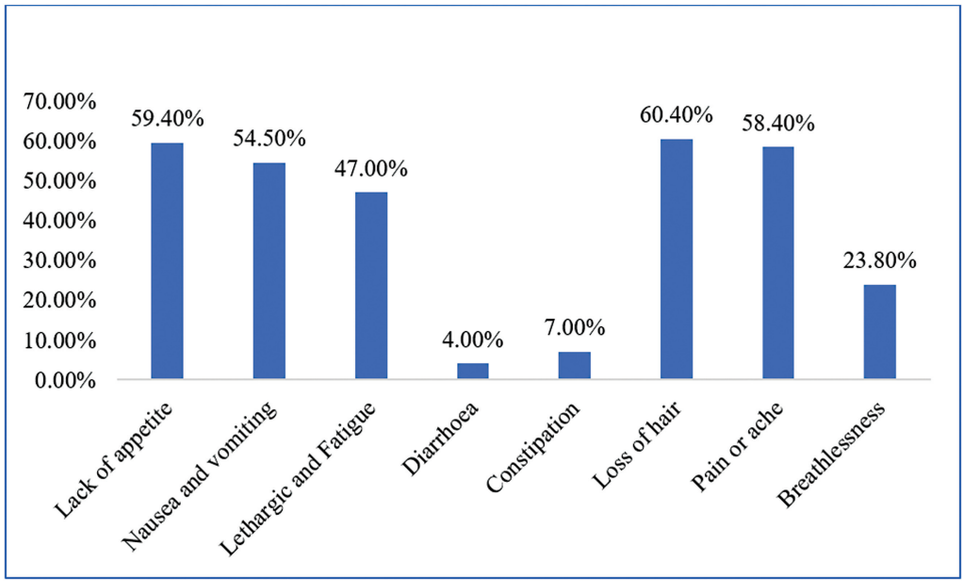

Fig. 1 Physical needs of the study participants.

Supportive care during chemotherapy was reported by 21.2% of the participants.

Total Needs of Patients

The overall score reflects participants' total needs assessed across all domains of the CNAT-CC questionnaire. The CNAT-CC has multiple items assessing needs in physical, psychological, hospital care, information, and practical domains.

Table 2 Psychological needs of the study participants

Psychological domain		Count *N*	Column %
Feeling of anxiety	No	67	66.3
	Yes	34	33.7
Feeling of depressed	No	91	90.1
	Yes	10	9.9
Feeling stressed during treatment	No	81	80.2
	Yes	20	19.8
Feeling loneliness	No	89	88.1
	Yes	12	11.9
Fear of recurrence	No	92	91.1
	Yes	9	8.9
Fear of hospitalization	No	88	87.1
	Yes	13	12.9
Fear of chemotherapy sessions	No	74	73.3
	Yes	27	26.7
Fear of death	No	101	100.0
	Yes	0	0.0

The overall score of the patients in the current study ranged from 34 to 62, with a mean of 47.72 ± 7.54.

Overall Needs of Patients

Most participants had moderate needs (67.3%) during their treatment course (►**Fig. 2**), based on the overall scores obtained from the different domains.

Factors Associated with Patient Needs

Sociodemographic factors associated with the participants' overall needs show that the family's socioeconomic status is associated with the overall needs with a chi-square value of 11.87 and a *p*-value of 0.01, which shows statistical significance.

Similarly, the type of family is associated with patients' overall needs with a chi-square value of 20.26 and a *p*-value of 0.001 that shows statistical significance (►**Table 3**).

The results showed that participants in both third and fourth stage cancer had moderate needs. Comorbidities were associated with greater needs, as participants with comorbid conditions tended to have moderate needs. The association between comorbidities and increased needs was statistically significant, with a *p*-value of 0.043.

Higher needs were also correlated with undergoing chemotherapy. Participants receiving chemotherapy were more likely to have moderate needs compared to other treatments. This relationship was statistically significant, with a chi-square value of 13.36 and a *p*-value of 0.004 (►**Table 4**).

Discussion

This study aimed to assess the needs of patients undergoing chemotherapy for cancer. Needs were assessed using a physical, psychological, care, and communication questionnaire. In the current study, 61.4% of the participants were female and 38.6% were male. Almost all (92.1%) participants

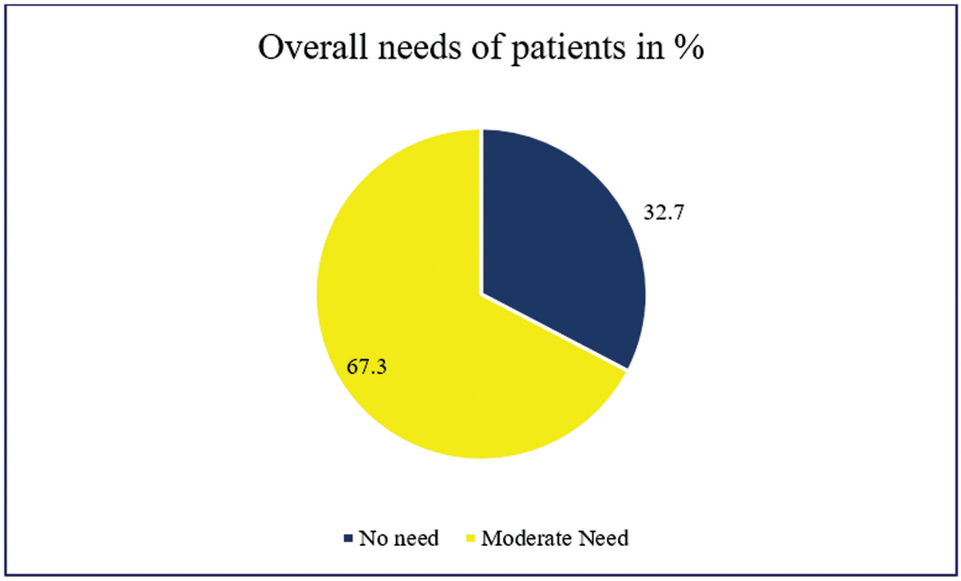

Fig. 2 Overall needs among the study participants.

Table 3 Association between sociodemographic variables and needs of the participants

Sociodemographic variables		Overall needs of patients							
		No need		Moderate need		High need			
		N	%	*N*	%	*N*	%	Chi-square value	*p*-Value
Gender	Male	17	51.5	22	32.4	0	0.0	3.442	0.064[a]
	Female	16	48.5	46	67.6	0	0.0		
Religion	Hindu	33	100.0	60	88.2	0	0.0	4.216	0.121[a]
	Christian	0	0.0	4	5.9	0	0.0		
	Muslim	0	0.0	4	5.9	0	0.0		
	Others	0	0.0	0	0.0	0	0.0		
Locality	Urban	11	33.3	35	51.5	0	0.0	2.947	0.086[a]
	Rural	22	66.7	33	48.5	0	0.0		
Marital status	Married	33	100.0	68	100.0	0	0.0	4.005	0.549[a]
	unmarried	0	0.0	0	0.0	0	0.0		
	Divorced	0	0.0	0	0.0	0	0.0		
	Separated	0	0.0	0	0.0	0	0.0		
	Widow/widower	0	0.0	0	0.0	0	0.0		
Education status of the head of the family	Illiterate	11	33.3	23	33.8	0	0.0		
	Primary education	1	3.0	5	7.4	0	0.0		
	Secondary education	5	15.2	6	8.8	0	0.0		
	High school education	3	9.1	13	19.1	0	0.0		
	Pre-university	7	21.2	14	20.6	0	0.0		
	Diploma/degree	6	18.2	7	10.3	0	0.0		
	Postgraduate	0	0.0	0	0.0	0	0.0		

(*Continued*)

Table 3 (*Continued*)

Sociodemographic variables		Overall needs of patients							
		No need		Moderate need		High need			
		N	%	*N*	%	*N*	%	Chi-square value	*p*-Value
Occupation status	Unemployed	12	36.4	12	17.6	0	0.0	4.710	0.194[a]
	Unskilled	3	9.1	11	16.2	0	0.0		
	Semiskilled	9	27.3	25	36.8	0	0.0		
	Skilled	9	27.3	20	29.4	0	0.0		
	Retired	0	0.0	0	0.0	0	0.0		
Living status	Living alone	0	0.0	0	0.0	0	0.0	–	–
	Living with spouse and children	33	100.0	68	100.0	0	0.0		
	Living with parents	0	0.0	0	0.0	0	0.0		
	Others	0	0.0	0	0.0	0	0.0		
Socioeconomic status of the family	7,008 and above	6	18.2	1	1.5	0	0.0	11.878	0.018[b]
	3,504–3,503	20	60.6	46	67.6	0	0.0		
	2,102–3,503	4	12.1	11	16.2	0	0.0		
	1,051–2,101	3	9.1	5	7.4	0	0.0		
	1,050 and below	0	0.0	5	7.4	0	0.0		

Note: Values are expressed as frequency and percentages.
[a]*p*-Value is by chi-square test.
[b]*p*-Value of less than 0.05 is considered to be statistically significant.

Table 4 Association between clinical profile and needs of the participants

		Overall needs of patients							
		No need		Moderate need		High need			
Case history		*N*	%	*N*	%	*N*	%	Chi-square value	*p*-Value
Stage of cancer	3	20	19.8	38	37.6	0	0.0	0.13	0.711
	4	13	12.9	29	28.7	0	0.0		
Type of tumor	Regional	1	1.0	3	3.0	0	0.0	0.14	0.93
	Localized metastasis	28	27.7	56	55.4	0	0.0		
	Metastasis	4	4.0	9	8.9	0	0.0		
	Unknown	0	0.0	0	0.0	0	0.0		
Comorbidities	Diabetes mellitus	0	0.0	3	3.0	0	0.0	9.34	0.043
	Diabetes mellitus and cardiovascular disease	0	0.0	3	3.0	0	0.0		
	Diabetes mellitus and hypertension	0	0.0	6	5.9	0	0.0		
	Hypertension	3	3.0	1	1.0	0	0.0		
	Nil	30	29.7	55	54.5	0	0.0		
Treatment	Surgery	0	0.0	0	0.0	0	0.0	13.36	0.004[a]
	Chemotherapy	22	21.8	45	44.6	0	0.0		
	Radiation	0	0.0	0	0.0	0	0.0		
	Surgery + chemotherapy	2	2.0	13	12.9	0	0.0		
	Chemotherapy + radiation	0	0.0	6	5.9	0	0.0		
	Surgery + chemotherapy + radiation	9	8.9	4	4.0	0	0.0		

Table 4 (*Continued*)

		Overall needs of patients							
		No need		Moderate need		High need			
Case history		*N*	%	*N*	%	*N*	%	Chi-square value	*p*-Value
Type of cancer	Acute leukemia	2	2.0	4	4.0	0	0.0	6.77	0.561
	Breast cancer	5	5.0	8	7.9	0	0.0		
	Colon cancer	0	0.0	2	2.0	0	0.0		
	Esophageal cancer	1	1.0	10	9.9	0	0.0		
	Leiomyosarcoma	1	1.0	2	2.0	0	0.0		
	Lung cancer	11	10.9	23	22.8	0	0.0		
	Ovarian cancer	1	1.0	4	4.0	0	0.0		
	Rectal cancer	9	8.9	9	8.9	0	0.0		
	Stomach cancer	3	3.0	6	5.9	0	0.0		

Note: Values are expressed as frequency and percentages, Regional: Tumor confined to the primary site and its surrounding tissues, possibly involving nearby lymph nodes. Localized metastasis: Tumor localized at the primary site with evidence of metastasis to regional lymph nodes. Metastasis: Presence of distant metastasis beyond the primary site.
[a]*p*-Value is by chi-square test, and a *p*-value of less than 0.05 is considered to be statistically significant.

were Hindu, 4% were Muslim, and 4% were Christian. Among the participants, 54.5% were from rural areas and 45.5% were from urban areas. In the current study, 33.7% of the participants were illiterate, while 12.9% had a diploma or degree. Most participants in the present study (33.7%) were semi-skilled and the least (13.9%) were unskilled.

Most of the participants in the current study have physical needs, as they had symptoms of loss of appetite, pain, nausea and vomiting, loss of hair, and diarrhea, and a few participants had breathlessness. The physical domain score was also high for all participants. This result aligns with findings from a study by Williamson et al, which showed patients had greater unmet needs related to physical symptoms arising during chemotherapy treatment.[10] Another cross-sectional study showed similar results, where most physical symptoms were nausea (23%), hair fall, pain, decreased appetite (40.1%), and anemia.[11]

In the psychological domain, most participants in the current study experienced anxiety and stress during chemotherapy. Some participants had a fear of chemotherapy sessions and skipped some of the sessions due to fear (26.7%). Few participants (11.8%) felt lonely during the treatment, and 8.9% feared cancer recurrence even after the chemotherapy. According to some participants in the current study, their fear of recurrence was also related to the high cost of treatment. Chaturvedi mentioned that depression (13–40%) and anxiety are cancer patients' most common psychiatric disorders.[12] Another cross-sectional study in North India shows that most participants had depression (55.7%), and the results concur with the current study (9.9%).[13]

The hospital domain score was lower in the present study; however, participants expressed overall satisfaction with the care provided by doctors and nurses, the availability of health care professionals during emergencies, and the prompt response to any adverse reactions during chemotherapy. The findings align with a study conducted in Indonesia, where chemotherapy patients reported high self-satisfaction with care and a strong fulfillment of their needs (98%).[14]

Patients had a moderate need (20.8%) for chemotherapy information. A moderate need (77.2 %) was observed during chemotherapy for information regarding adverse drug reactions. Five percent of the participants felt they needed information about government or private financial schemes concerning emergencies and self-management of adverse drug reactions. Information on the current state of illness, contact information for the treating physician, and the total cost of chemotherapy, were moderately needed by participants. The results of our study are contrary to those reported by Meredith et al, who observed that 79% of cancer patients wanted information about cancer and chemotherapy.[15] In a systematic review by Tariman et al, prognosis, diagnosis, and treatment options were identified as the top three information needs.[16] Another cross-sectional study conducted by Mekuria et al, it was observed that the information about the particular type of cancer and the disease staging is the most important to 67% of cancer patients, followed by 63.3% who want to know about the side effects of chemotherapy and how to deal with them, and 51.8% who want to know about prognosis (survival).[17]

In the current study, 19.8% of participants mentioned needing family support during chemotherapy. In most cases (43.6 %), participants required financial assistance. Transportation services were required by 35.6% of the participants to attend chemotherapy sessions and 21% of participants reported requiring supportive care during chemotherapy.

Similar results were found in a study by Longo et al, where the burden of treatment cost and the supportive care from the family members are the major unmet needs in chemotherapy patients.[18]

In the current study, socioeconomic status and family type were associated with moderate need during chemotherapy. The findings were similar to those of a study conducted in South India comparing sociodemographic factors and the clinical extent of cancer.[19] The current study showed that most participants had moderate needs (67.3%) during treatment.

The current study provides valuable insights into the specific needs of cancer patients undergoing chemotherapy. By understanding and addressing these needs, health care providers can optimize patient-centered care and enhance patients' overall quality of life undergoing chemotherapy. Further research should explore tailored interventions to meet these needs and evaluate their impact on patient outcomes. By implementing these strategies, health care professionals can contribute to better outcomes and improved experiences for patients with cancer undergoing chemotherapy.

Limitations of this study include its cross-sectional design, preventing causal inferences, potential biases associated with self-reported data, limited generalizability due to the study's specific geographic focus, and the absence of a control group for comparative analysis. The 2-month study duration may not capture long-term variations in patients' needs. Despite these limitations, the study provides valuable insights into chemotherapy needs, offering a basis for future research and interventions.

Conclusion

The study findings underscore the moderate needs of cancer patients undergoing chemotherapy, particularly in the physical and psychological domains. These results emphasize the importance of developing new plans or policies to alleviate the burden and improve the quality of life of individuals receiving cancer chemotherapy.

Patient Consent

Informed consent was obtained from each participant before the commencement of the study.

Conflict of Interest

None declared.

Acknowledgments

We sincerely thank the nursing staff and interns who were posted at the Department of Medical Oncology for their invaluable assistance in the data collection process. Their support and cooperation were instrumental to the successful completion of this study.

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Real-World Evidence Data on Adverse Reactions to Infusion of Thawed Hematopoietic Progenitor Cells: Retrospective Analysis from a Single Center in India

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Ind J Med Paediatr Oncol 2025;46:57–63.

Abstract

Introduction Adverse reactions (ARs) occur during infusion of thawed hematopoietic progenitor cells (HPCs) either due to infusion or its contents. There is sparse literature on it in the world and none in India. Therefore, we retrospectively analyzed ARs occurring during and within 1 hour of infusion of thawed HPCs.

Objective This study aimed to evaluate the prevalence of adverse reactions associated with the infusion of cryopreserved hematopoietic progenitor cells (HPC) and to categorize the types of adverse reactions observed in HPC transplant recipients during its infusion.

Materials and Methods This study was done in a tertiary-care center, between 2019 and 2022. Data collected included age, gender, diagnosis, specifications of contents of infusion product (volume of product, volume of dimethyl sulfoxide per kg body weight, total nucleated cell count per microliter, and viability of CD 34+ cells), pretreatment given, and ARs, if any from the procedure records and the hospital information system.

Results The present study included 55 transplant patients, and the commonest diagnosis was Hodgkin lymphoma. All were prophylactically hydrated and premedicated as per institutional protocol. AR was seen in 56.36% ($n = 31$); the commonest type of ARs was nausea ($n = 26$) followed by vomiting ($n = 13$), abdominal pain ($n = 4$), shivering ($n = 3$), transient tachycardia ($n = 2$), transient hypotension ($n = 2$), and hematuria ($n = 1$). All ARs were managed clinically by giving symptomatic treatment. No patients required intensive care, and there were no deaths or aborted procedures. Characteristics of infusion products had no significant correlation to ARs.

Keywords
- adverse reactions
- infusion
- transplant
- hematopoietic progenitor cell

article published online
July 22, 2024

DOI https://doi.org/10.1055/s-0044-1788311.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusions To the best of the author's knowledge, this is the first such study from India. We report an overall incidence of ARs of 56.36%, which is similar to the previously published data on ARs during thawed HPC infusions. AR is a common occurrence and can be managed medically and symptomatically.

Introduction

Hematopoietic progenitor cell (HPC) transplant is done for various indications, both benign and malignant; benign disorders such as thalassemia major, sickle cell anemia, aplastic anemia, and malignant disorders such as acute myeloid leukemia, myelodysplastic syndromes, myeloproliferative disorders, acute lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, and lymphomas.

There are three major forms of HPC transplants performed clinically: (1) autologous transplantation, in which the patient serves as a self-donor; (2) allogeneic transplantation, from another person, and (3) cord blood transplant.[1] In autologous transplantation, the reinfusion of the patient's HPCs allows for the recovery of the marrow following high-dose myeloablative chemotherapy and is, hence, also known as bone marrow rescue.[2]

While cord HPC is infrequent, the commonest transplant in clinical settings is allogeneic HPC transplantation, where the healthy donor provides HPC either from bone marrow (HPC-M) or from peripheral blood through an apheresis procedure (HPC-A).[2] HPC-A has almost replaced HPC-M because of the ease and safety of collection and quicker recovery of granulocytes and platelets from the apheresis procedure compared with bone marrow collection.[1]

Harvested HPC-A can be stored at 4°C for up to 2 days in certain cases, such as multiple myeloma, where patient conditioning is quicker.[3] It must be cryopreserved in cases such as lymphoma, where patient conditioning takes 6 to 7 days or the HPC product must be shipped to a different state or country. Advancement in HPC processing over the years has led to the ability to cryopreserve cells for long-term storage, wherein stem cells can be collected in advance, cryopreserved, and then infused after the administration of myeloablative doses of chemotherapy or chemoradiotherapy in the recipients.[4]

Once the patient is conditioned, the HPC is infused to reconstitute the hematopoietic system. Such infusion of HPCs is generally a safe procedure, but these infusions have the potential to cause adverse reactions (ARs). These range from mild reactions such as nausea, vomiting, fever, flushing, chills, and cough to severe reactions affecting cardiovascular, respiratory, and neurological systems.[5] Mild ARs are more common than severe or life-threatening ARs.[5]

ARs due to the infusion of thawed HPCs are not well-documented globally, and there is a lack of literature on this in India. Therefore, we observed and analyzed ARs occurring within 1 hour of infusion in transplant recipients in our retrospective cohort of 4 years.

Materials and Methods

Settings

This observational analytical study was conducted between 2019 and 2022 at a tertiary care hospital in India. The study population included all patients who were transfused thawed HPC during the study period.

Collection and Cryopreservation

HPCs were collected through an apheresis (HPC-A) procedure using an automated cell separator machine (Com.Tec [Fresenius Kabi AG, Bad Homburg, Germany]) from donors (allogeneic transplant) or patients (autologous transplants). The donors/patients were mobilized using a granulocyte-colony stimulating factor with/without CXCR4 inhibitor (Plerixafor). After the target CD34 positive cell dose was achieved (4–6 million cells/kg body weight for allogeneic transplant and 2–4 million cells/kg body weight for autologous transplant), the collected HPC-A product was transported to an outside National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited Good Laboratory Practices (GLP)-certified cellular-therapy laboratory for cryopreservation. The HPC-A product was centrifuged, and excess plasma was expressed off.

The product was then transferred into freezing bags, and cryoprotectant solution (100% dimethyl sulfoxide [DMSO]) and sedimentation agent (6% hydroxyethyl starch [HES]) were added according to the product volume. The final concentration of DMSO was 5%.[6,7] A small aliquot (1 mL) was separated to serve as a control for the cryopreservation process. The final HPC-A product was frozen using a controlled rate freezer and then cryopreserved at less than −196°C in a vapor-phase liquid nitrogen storage freezer.

The viability of the infusion product was done twice, prefreezing and preinfusion by flow cytometry using 7-aminoactinomycin D (7-AAD). These tests were done at the same laboratory that performed the cryopreservation (NABL-accredited GLP certified). The final CD34 infusion dose was based on both postthaw viability and flow cytometry CD34 counts.

Thawing and Infusion

On the day of the transplant, cryopreserved HPC product was transported to the transplantation center in a

temperature-monitored liquid-nitrogen cryoshipper (MVE Cryoshipper, MVE Biological Solutions, LLC, United States). The cryopreserved HPC product was thawed bedside to 37° C using a dry-plasma thawer (Barkey Plasmatherm V, Barkey GmbH & Co. KG, Germany). The process was done under sterile conditions by a transfusion medicine specialist, in the presence of a transplant physician.

The HPC infusion was performed in a positive pressure room fitted with a high-efficiency particulate air filter. All the patients were prophylactically hydrated (10–15 mL/kg body weight, up to 1 L) and premedicated with an antihistaminic (injection Pheniramine maleate 2 mL stat) and an antipyretic (Paracetamol infusion 10 mg/kg body weight, maximum dose of 1 g) as per institutional protocol, 30 minutes before the start of infusion.

The infusion was initiated through a peripherally inserted central catheter (line) in all patients immediately after thawing at the rate of 20 mL/min. The rate of infusion was increased up to 50 mL/min if the patient had no AR in the first 10 minutes. The patients were monitored for vital signs including blood pressure, pulse, respiratory rate, and oxygen saturation during and after the infusion.

Adverse Reaction Definition/Record

ARs were defined according to the Common Terminology Criteria for Adverse Events criteria.[8] Vital signs included hypotension (systolic pressure $<$ 90 mm Hg, if previously normotensive or a decrease in systolic pressure of 20 mm Hg), hypertension ($>$ 150/100 mm Hg if previously normotensive or an increase $>$ 20 mm Hg in diastolic blood pressure), bradycardia (heart rate $<$ 60 bpm), tachycardia (heart rate $>$ 100 bpm), arrhythmia, hypoxia (oxygen saturation $<$ 95%), tachypnoea (respiratory rate $>$ 20), fever (temperature $>$ 38°C), and hypothermia (temperature $<$ 35°C).

Vital signs were recorded at the start of infusion and at 15-minute intervals thereafter till 1-hour postinfusion. Any AS occurring during and within 1-hour postinfusion was documented in the procedure sheet. Management was done according to the institutional standard operating procedures.

Postinfusion Protocol

Reverse barrier nursing was practiced according to the institutional protocol. Patient monitoring was done for laboratory parameters at defined frequency (complete blood counts and electrolytes once a day; liver function tests, renal function tests, and blood glucose twice a week; blood culture as and when deemed necessary). Antimicrobial prophylaxis included antibacterial (levofloxacin), antifungal (fluconazole), and antiviral (acyclovir) activities.

Data Collection

Data collected included patient/recipient age ($\leq$18-year-old were considered in the "children" subgroup), gender, diagnosis, details of the infusion product (like volume of infusion product, volume of DMSO per kg body weight, total nucleated cell count (TNCC) per microliter, viability of CD 34+ cells), pretreatment given, and AS, if any. The data were collected from the procedure sheet filled at the time of infusion and from the hospital information system (HIS).

Inclusion and Exclusion Criteria

All the patients who underwent infusion of thawed HPCs and filled procedure sheets were included in the study. Any patient with an incompletely filled procedure sheet was excluded from the study.

Statistical Analysis

Data were analyzed, and mean, median, and range were calculated using Microsoft Excel software and SPSS Software version 23.0 (SPSS Inc., Chicago, Illinois, United States); p-values $<$0.05 were considered significant.

Ethical Approval

The study has been approved by the Institutional Ethics Committee on 29.03.2023, Reference no: 1513/2023 (Academic). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Demographics and Patient Characteristics

Fifty-five patients were transfused thawed HPC-A during the study period, and all of them were included in the study analysis. There were 32 males and 23 females (M:F was 1.39:1). Twenty-nine were adult patients (52.72%), and twenty-six were children (47.27%). The most common diagnosis for which these patients were undergoing HPC transplant was Hodgkin lymphoma followed by diffuse large B cell lymphoma. All patients were transfused infusion volume on a single day.

Complete patient characteristics are mentioned in ►**Table 1**.

Characteristics of the Infusion Product

Characteristics of the thawed HPC-A product transfused to the patients undergoing transplant were studied and included the total volume of the product transfused, volume of infusion product per kg body weight, number of CD34 cells, volume of DMSO, TNCC, and viability. The median viability by 7-AAD prefreezing was 99%. The difference between median viability at prefreezing and preinfusion was 6.6% (99–92.4%). The characteristics of the infusion product are mentioned in ►**Table 2**.

Adverse Reactions

►**Fig. 1** shows the incidence of AR among different study groups. The overall incidence of AR was 56.36% (n = 31); the most common type of AS was nausea (n = 26) followed by vomiting (n = 13). The types of AR that occurred in the study population are demonstrated in ►**Fig. 2**.

Table 1 Patient characteristics

Patient characteristics	*n* (%)
Gender	
Female	32 (58.2%)
Male	23 (41.8%)
Age group (in years)	
≤18	26 (47.27%)
19–30	12 (21.81%)
31–50	11 (20%)
>50	06 (10.90%)
Diagnosis	
Hodgkin lymphoma	16 (29.1%)
Diffuse large B cell lymphoma	11 (20%)
Rhabdoid tumor	06 (10.9%)
T cell lymphoma	03 (5.50%)
Non-Hodgkin lymphoma, Ewing's sarcoma, thalassemia major	02 cases each
Germ cell tumor, lymphoma, GI lymphoma, primary CNS lymphoma, neuroblastoma, medulloblastoma, multiple myeloma, osteosarcoma, sickle cell anemia, Wilm's tumor, ALL	01 case each
Type of transplant	
Autologous	49 (89.09%)
Allogeneic	06 (10.90%)

Abbreviations: ALL, acute lymphocytic leukemia; CNS, central nervous system; GI, gastrointestinal.

Management of Adverse Reactions

All AR were managed clinically, as shown in ►**Table 3**. No patients required intensive care, and there were no deaths or aborted procedures.

Factors Affecting Adverse Reactions

The possible factors affecting AR in recipients like the volume of infusion product, volume of DMSO per kg body weight, TNCC per microliter, and viability of CD 34+ cells were analyzed using a chi-square test, and these had no significant correlation to AR.

Discussion

The present study analyzed the incidence and classified the AR occurring during the infusion of thawed hematopoietic progenitor cells. To the best of the author's knowledge, this is the first such study from India. There are several previous studies from India[9–12] that have reported long-term complications and transplant outcomes after infusion of cryopreserved HPC. Only one of these studies by Setia et al[12] briefly mentions ASs during the infusion. However, studying the ASs during the infusion of thawed HPC was not an objective of any of these studies.[9–12]

In the present study, the prevalence and type of ASs during and immediately after the "infusion" of thawed HPCs have been collated, analyzed, and discussed. We report an overall incidence of AR of 56.36%, which is similar to the previously published data on ASs during thawed HPC infusions.[5,8,13,14] In addition, 30.90% of patients had more than one AR. The most common AR reported in our study were gastrointestinal symptoms, mainly nausea (50.98%) followed by vomiting (25.49%).

Mobilized stem cells are harvested from the peripheral blood with a continuous-flow blood cell separator apheresis system (HPC-A). High-dose chemotherapy causes myeloablation of the normal marrow cells, and restoration of hematopoiesis is accomplished by infusion of HPC, thereafter. The duration from HPC-A collection to infusion might vary depending on the type of transplant and the conditioning regimen required in each case. When harvested HPC-A must be cryopreserved until the date of graft infusion, the most used cryoprotectant is DMSO,[6] an agent that has a known spectrum of adverse effects. ARs have been related to the amount of DMSO in the HPC-A.[7] Currently, there are no guidelines for the use of DMSO in stem cell cryopreservation; however, DMSO at 5% concentration is used by most centers.

Gokarn et al[15] studied the effect of long-term cryopreservation using 4.35% DMSO with methyl cellulose and uncontrolled rate freezing in a mechanical freezer (−80°C) on the viability of CD34+ HPCs. Twenty-six HPC harvest samples with a median cryopreservation duration of 6.6 years were studied. The median viability of post-thaw HPCs was >80% using trypan blue exclusion and flow cytometry-based 7-AAD methods. The clonogenic potential of postthaw stem cells was studied using a colony-forming unit assay, which

Table 2 Characteristics of the infusion product

Characteristics	Mean ± SD	Minimum	Maximum
Total volume transfused (mL)	334.8 ± 203.1	21.5	792.0
Infusion product per kg body weight	6.1 ± 3.1	0.6	19.1
CD 34+ cells per kg body weight	7.1 ± 6.1	1.7	39.0
Volume of DMSO (mL)	32.4 ± 17.1	4.0	72.0
TNCC × 10^3 / μL	215.5 ± 123.4	9.0	469.0
Viability (%)	92.4 ± 4.6	76.0	99.0

Abbreviations: DMSO, dimethyl sulfoxide, SD, standard deviation; TNCC, total nucleated cell count.

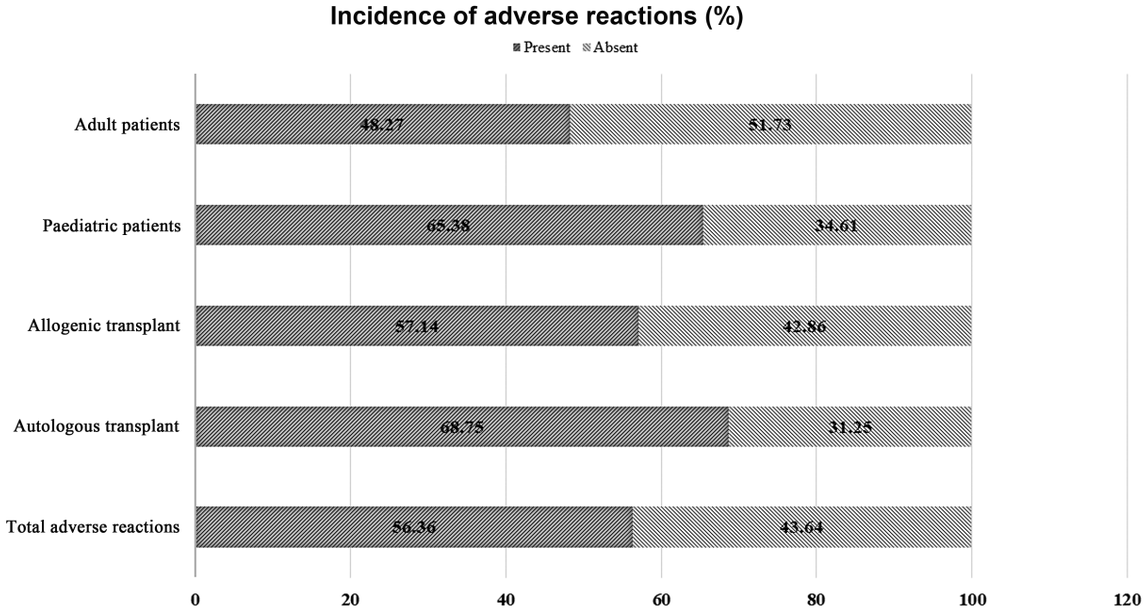

Fig. 1 Incidence of adverse reactions in different study groups.

yielded a good proliferation and differentiation potential in postthaw HPCs.

Types of Adverse Reactions Occurring during Infusion of Thawed Hematopoietic Progenitor Cell

AR was reported in 56.36% of infusions. ►**Table 4** demonstrates the incidence of AR in the present study in comparison with the other published data. Among the AR reported in our patients, nausea (50.98%) was the most frequent AR followed by vomiting (25.49%). These data were in concordance with that published by Truong et al, where they reported nausea as the most common AR (42%) followed by vomiting (28%).[5] Otrock et al also reported nausea and/or vomiting in 38.1% of the cases.[14]

Cordoba et al[13] reported allergic reactions as the most common AR, occurring in 43.75% cases. Similarly, Otrock et al[14] reported facial flushing in 39.4% of the cases. Cardiovascular symptoms were reported to be highest in the study published by Vidula et al,[8] in 48% of the study population. Genitourinary reactions were the least common

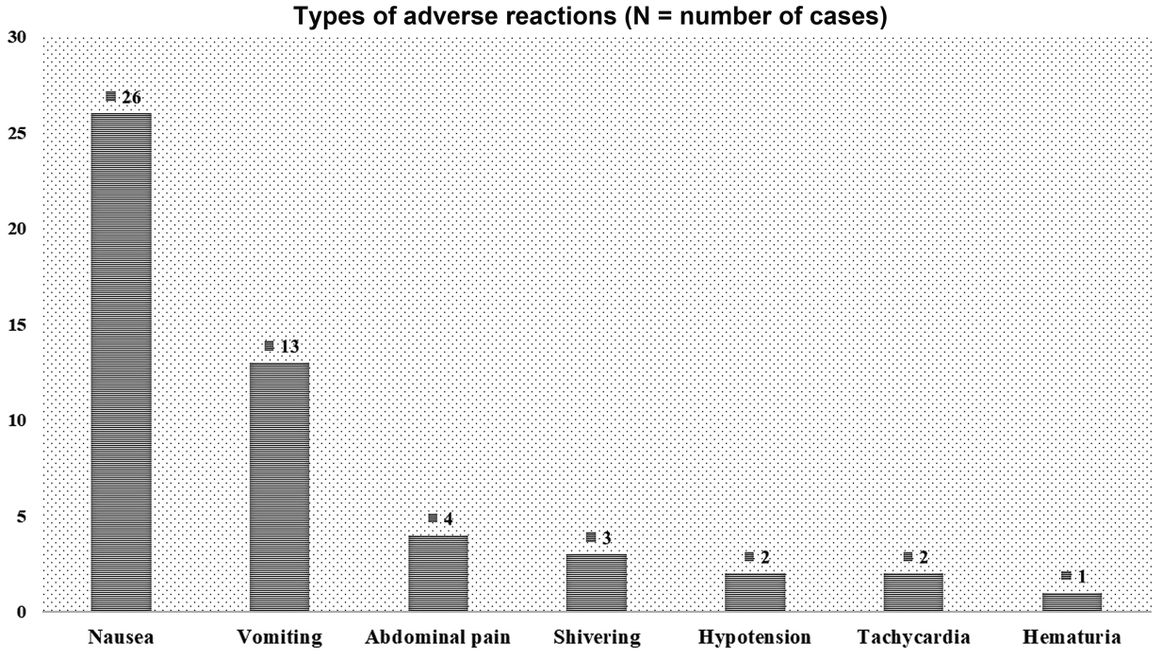

Fig. 2 Types of adverse reactions in the study population.

Table 3 Adverse reactions with corresponding management given at the time of reaction

Adverse reaction	Management	Median time to resolution
Nausea, vomiting	Antiemetic given stat	16 min
Transient tachycardia, transient hypotension, shivering	Slowing of infusion rate till the reaction subsided	28 min
Hematuria	Double maintenance fluids given till the reaction subsides	110 min
Abdominal pain	Antispasmodic given stat	36 min

AR in our study with hematuria occurring in 1.96% of the patients. There were no cases of reactions requiring intensive care management, no deaths occurred, and no procedure was aborted.

Some of the centers wash the cryopreserved thawed HPCs before the infusion to remove DMSO. Solves et al[16] studied and compared the incidence of AR in patients receiving thawed and washed HPC (peripheral blood and cord) and patients receiving noncryopreserved HPC. Before infusion, the cryopreserved HPCs were washed with a solution containing albumin, acid citrate dextrose, and dextran solution in an IBM-COBE 2991 cell processor (Gambro BCT, Lakewood, Colorado, United States). They reported a statistically insignificant difference ($p = 0.114$) between the two groups and concluded that AR occurred in a significant number of patients after thawed and washed (39.2%) and noncryopreserved (23%) HPC infusions. AR were mild, nonspecific, and well-controlled with nausea, vomiting, and fever being the most common AR.

Factors Affecting Adverse Reactions

Martín-Henao et al[17] studied the correlation of the number of granulocyte cells in the leukapheresis product to the occurrence of ASs during transfusion of thawed HPCs. They reported that the volume of DMSO kg, volume of red blood cells kg, number of nuclear cells (NCs) kg, and number of granulocytes kg in the infused graft were significant for the occurrence of AR. The grade of AR also correlated with the number of granulocytes.

Similarly, Otrock et al found that granulocyte content was an independent risk factor for AR. Another independent predictor of AR in the same study was the volume of graft

Table 4 Adverse reactions in the present study and comparison with published reports

S. No.	Year of publication	Study	Concentration of DMSO infused	Sample size (n)	Incidence (%)	Type of adverse reactions
1.	Present study		5%	55	56.36%	50.98% ($n = 26$) nausea 25.49% ($n = 13$) vomiting 7.84% ($n = 4$) abdominal pain 5.88% ($n = 3$) shivering 3.92% ($n = 2$) transient tachycardia 3.92% ($n = 2$) transient hypotension 1.96% ($n = 1$) hematuria
2.	2007	Cordoba et al[13]	5–10%	144	67.36	43.75% allergic reactions 25% gastrointestinal symptoms 20.83% respiratory symptoms 11.81% cardiovascular symptoms 3.47% neurological symptoms
3.	2015	Vidula et al[8]	10%	460	56.7	48% cardiovascular symptoms 14.3% respiratory symptoms 4.6% gastrointestinal symptoms 3.5% constitutional symptoms 1.1% neurological symptoms 0.22% genitourinary symptoms
4.	2016	Truong et al[5]	10%	213	55	Most common reaction was nausea (42%), followed by vomiting (28%)
5.	2017	Otrock et al[14]	10%	1,269	37.8	39.4% facial flushing 38.1% nausea and/or vomiting 29% hypoxia requiring oxygen 16.7% chest tightness 12.1% cough 8.3% shortness of breath 7.3% cardiovascular symptoms

Abbreviations: DMSO, dimethyl sulfoxide.

infused per body weight. Infused granulocytes were significantly higher in the infusions with AR.[14]

For patients receiving allogeneic transplants, Vidula et al reported that the factor of greatest significance was greater red blood cell volume. They found that a greater granulocyte volume had a borderline association with the occurrence of AR.[8]

In the present study, the authors did not find a statistically significant correlation between characteristics of the infusion product that have previously been associated with AR, such as the number of granulocytes and DMSO volume or infusion rate and incidence of AR. A larger prospective study is needed to establish the relationship between the characteristics of the infusion product and the occurrence of AR.

Conclusion

ASs are a common occurrence during the infusion of thawed HPCs (56.36%) and can be managed medically and symptomatically.

Note

The manuscript has been read and approved by all the authors and the requirements for authorship have been met. Each author believes that the manuscript represents honest work.

Author's Contributions

A.K.T. conceptualized and designed the study protocol, screened eligible studies previously published and analyzed the data. G.A. and S. Pabbi contributed to writing the report, analyzing data, and interpreting the results. S. Pawar, S. Golia, and S. Gupta contributed to extracting data from the procedure sheet and HIS, writing the report, and updating the reference lists. G.R. provided technical support during the conduct of the study. N.S. and S.Y. contributed to manuscript editing and review. All authors reviewed and approved the final manuscript.

Patient Consent

Informed consent was obtained from each patient before commencing treatment. Patient identifiers were removed and complete confidentiality was maintained. There was no study-specific consent since anonymised data was used for this observational analysis. Institutional review board (IRB) gave a waiver for study-specific consent.

Funding

None.

Conflict of Interest

None declared.

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Structure-Based Virtual Screening and Protein–Protein Docking Analysis of ERBB2 and Associated Proteins for Pediatric Cancer Therapeutic Approaches

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Ind J Med Paediatr Oncol 2025;46:64–70.

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Abstract

Introduction The Erythroblastosis Oncogene B homolog 2 (ERBB2) protein, also known as human epidermal growth factor receptor 2 (HER2), is a key player in cancer growth, especially in neuroblastoma and gastric cancers. Targeting ERBB2 has led to successful therapies, making it an important focus in cancer research with the potential to improve treatment for HER2-positive cancers.

Objective The primary goal of this research is to employ a multifaceted computational approach to identify potential drug candidates targeting ERBB2. We aim to combine virtual screening, protein–protein docking, and functional partner prediction to provide insights into the molecular interactions and potential efficacy of the identified compounds. Additionally, we intend to assess the safety profiles of these compounds using advanced toxicity prediction tools.

Materials and Methods Relevant protein sequence and structural data for ERBB2 and epidermal growth factor receptor (EGFR) were sourced from publicly available databases. Potential inhibitors from the Enamine and LifeChemicals databases were identified through virtual screening using AutoDock Vina. Functional partners of ERBB2 were explored using STRING, KEGG, and REACTOME servers. The identified compounds were subjected to toxicity prediction using the ProTox-II server.

Results Virtual screening led to the selection of 10 compounds with favorable binding energies (–8.346 to –6.296 kcal/mol) and specific amino acid interactions (Thr5, Arg412, Leu414, and Ser441) with the receptor. On the other hand, EGFR was identified as the best functional partner for ERBB2. The EGFR residues Gln408, Lys463, Phe412, and Asp436 found key residues for the complex formation. The toxicity prediction analysis revealed that the majority of compounds exhibited acceptable safety profiles, although a subset of compounds showed lower prediction scores, suggesting the need for further consideration.

Conclusion This comprehensive computational approach, integrating virtual screening, protein–protein docking, functional partner identification, and toxicity prediction, offers a systematic framework for efficient drug discovery. The identification of potential lead compounds targeting ERBB2, with emphasis on both binding affinity and safety, underscores the significance of such an approach in streamlining the drug development process. By prioritizing compounds with promising efficacy, functional

Keywords
- AutoDock Vina
- docking
- ERBB2
- EGFR
- toxicity prediction
- virtual screening

article published online
September 2, 2024

DOI https://doi.org/10.1055/s-0044-1786163.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

relevance, and acceptable toxicity profiles, this study advances our understanding of potential therapeutic agents, enhancing the likelihood of successful translation from computational predictions to real-world drug candidates.

Introduction

The ERBB2 protein, also known as human epidermal growth factor receptor 2 (HER2), plays a pivotal role in cell proliferation, survival, and differentiation.[1] Dysregulation or overexpression of ERBB2 has been linked to various cancers, such as neuroblastoma, gastric, breast, and ovarian cancers, making it an attractive therapeutic target.[2] Human ERBB2 was initially identified as an oncogene in rat brain tumors induced by chemicals. Subsequent analysis of human tissues revealed ERBB2 amplification in specific cases of salivary carcinomas and breast cancers with poor prognosis. These early findings sparked significant interest in ERBB2's role in human cancer, leading to a multitude of studies investigating the biology and clinical relevance of ERBB receptor signaling.[3,4] In recent years, structure-based virtual screening and in silico analysis have emerged as powerful approaches to identifying potential inhibitors for specific protein targets.

This comprehensive study aimed to identify novel inhibitors for the ERBB2 protein through structure-based virtual screening and in silico analysis. Leveraging the wealth of available protein structural data, computational tools, and advanced algorithms, we sought to identify small molecules with the potential to interact with key binding sites on ERBB2 and disrupt its activity.

By employing state-of-the-art computational techniques, including molecular docking, protein–protein docking, and binding free energy calculations, we conducted an extensive screening of a diverse chemical library. Our focus on ERBB2-specific binding sites aims to prioritize compounds with high binding affinities and favorable amino acid interactions, thereby increasing the likelihood of successful inhibition. The identification of novel ERBB2 inhibitors holds promise for developing targeted therapies that can effectively combat cancers associated with ERBB2 dysregulation.[5] These findings may contribute significantly to advancing personalized medicine and improving the overall efficacy of cancer treatments.

Overall, this study represents a crucial step toward harnessing the power of computational approaches to expedite the discovery of new and potent ERBB2 inhibitors, fostering advancements in precision oncology and targeted therapeutics. The implications of these findings in the context of cancer therapy and future directions for experimental validation and drug development are also discussed.

Methodology

Data Collection

Relevant protein sequence and structural data for ERBB2 and other targets were sourced from publicly available databases and repositories, including PubMed, RCSB-PDB, and UniProt.[6] Our primary objective was to identify potential inhibitors from diverse natural databases, such as Enamine and LifeChemicals for ERBB2.[7,8] These databases are distinguished for their wealth of natural compound derivatives and medicinal value. The compounds pinpointed through virtual screening present viable candidates for subsequent experimental studies. The compound library was downloaded from the official website of the respective chemical compound database. A protein–protein docking protocol and pertinent data were acquired through a comprehensive literature survey.

Protein and Ligand Preparation

Protein and ligand preparation are essential steps in molecular docking studies, and AutoDock Vina serves as a powerful tool for this purpose. In the initial phase, the protein structure is prepared by removing any water molecules, heteroatoms, and cocrystallized ligands that are not part of the binding site. The protein is then assigned appropriate atom types, charges, and torsion angles, and polar hydrogens are added.[9] Careful attention is given to the correct protonation states of ionizable residues, ensuring accuracy in the simulation.

On the other hand, ligands are prepared by removing any counterions, water molecules, or other nonessential entities. The ligand's three-dimensional structure is refined by optimizing bond lengths, angles, and torsion angles. Proper charges, atom types, and hybridization states are assigned to the ligand's atoms, ensuring compatibility with the chosen force field. Additionally, for flexible ligand docking, multiple conformations of the ligand were generated for a single ligand to explore potential binding modes. Based on the binding energy calculated for each ligand conformation, the potential ligand and its binding pose were considered.

Overall, this meticulous preparation of both protein and ligand ensures a reliable and accurate docking simulation with AutoDock Vina, enabling the exploration of protein–ligand interactions and the prediction of potential binding poses, ultimately aiding in drug discovery and future molecular design efforts.

Structure-Based Virtual Screening

Structure-based virtual screening is a valuable computational approach employed to identify potential drug candidates by predicting their binding affinities to a target protein (ERBB2), using the AutoDock Vina tool.[10] In this study, the LifeChemicals and Enamine compound databases were utilized as valuable sources of diverse small molecules. The prepared protein structure and ligand molecules were utilized for the virtual screening studies.

The virtual screening was conducted by docking each compound from the LifeChemicals and Enamine databases into the active site of the ERBB2 protein. AutoDock Vina exhaustively

sampled binding poses and ranked the compounds based on their calculated binding energies, reflecting the strength of their potential interactions with the protein. The top-ranking compounds, with the most favorable binding energies, were further analyzed to assess their predicted binding modes, hydrogen bonding patterns, and key interacting residues within the binding site. Default protocols of the AutoDock Vina were implemented throughout the virtual screening analysis.

This structure-based virtual screening using AutoDock Vina, coupled with the utilization of the LifeChemicals and Enamine databases, provided a systematic and efficient means to prioritize promising small molecules for potential ERBB2 inhibition.[11,12] The results from this study contribute valuable insights into the realm of drug discovery, guiding experimental efforts toward the identification and development of novel therapeutic agents targeting ERBB2-associated diseases.[13]

Functional Partner Discovery with Bioinformatics Tools

Functional partners in a pathway are crucial components that interact with each other to execute specific biological processes, such as cancer pathogenesis. Identifying these partners is essential for understanding the intricate molecular mechanisms that govern cellular functions. Tools and servers such as STRING,[14] KEGG,[15] and REACTOME[16] provide valuable resources to unravel these interactions and uncover the network of relationships within a pathway. STRING is a powerful bioinformatics resource that specializes in predicting protein–protein interactions. It integrates various sources of experimental and computational data to construct a comprehensive network of functional associations between proteins. KEGG is a widely used resource for understanding biological pathways and the interactions among genes and proteins in various organisms. REACTOME is another valuable resource for pathway analysis, providing a curated knowledge base of biological pathways. Consolidating all the results and identifying the potential functional partner will be subjected to further computational analysis.

Protein–Protein Docking

The protein–protein docking between two or more proteins was performed using the HADDOCK 2.4 server, an advanced computational tool specifically designed for modeling macromolecular interactions.[17] The main objective of this docking study was to predict the potential binding modes and interface interactions between these two important proteins, which play crucial roles in signaling pathways and cellular processes. Parameters were set to define ERBB2 as the "receptor" and the identified functional protein as the "ligand," given their respective roles in the interaction.

Active residues, crucial for the protein–protein interaction, were defined based on the known literature and biological context. These active residues were set to be unbound and flexible during the docking simulations. The initial docking runs were performed using the rigid body docking mode, allowing for a global search of possible binding orientations. HADDOCK generated an ensemble of docking solutions for further refinement. The top-scoring docking solutions were selected for the semiflexible refinement stage. During this step, the side chains of the active residues were allowed to optimize their positions, employing a simulated annealing protocol. The resulting docked complexes were analyzed to identify the most probable binding mode, interface residues, hydrogen bonding, and hydrophobic interactions between ERBB2 and functional proteins.[5,18] The binding energy of the top-ranked solution was used as an indicator of the stability of the predicted complex.

Toxicity Prediction Analysis

The toxicity prediction of the identified lead compounds was performed using the ProTox-II server, a widely recognized computational tool specifically designed for predicting the potential toxicity of small molecules.[19] This step was crucial in the drug discovery process to assess the safety profile of the identified lead compounds before further experimental investigations. The top five potential lead compounds were selected based on their favorable binding energies and predicted binding modes from our structure-based virtual screening analysis. ProTox-II provided predictions for multiple toxicity endpoints, including mutagenicity, hepatotoxicity, carcinotoxicity, and others, using validated models. The predicted toxicity scores were interpreted, considering both the individual toxicity endpoints and the overall toxicity profile.[20] The toxicity predictions were critically analyzed in the context of the intended therapeutic application and the known safety standards for pharmaceutical compounds. This approach ensures that the lead compounds with the most promising efficacy and favorable safety profiles are advanced in the drug discovery pipeline, enhancing the overall success rate of the drug development process.

Ethics

No human participants/subjects were involved in this study.

Results

Virtual Screening Studies

The structure-based drug design study conducted using AutoDock Vina yielded promising results in the search for potential drug candidates from the Enamine and LifeChemicals databases. After rigorous filtering based on the Lipinski Rule of Five, which ensures drug-likeness and favorable pharmacokinetic properties, a total of 385,000 and 137,000 compounds were retained from the LifeChemicals and Enamine databases, respectively, for further analysis. The AutoDock Vina program automatically generates the grid map and presents clustered results to users in a transparent manner. Within Vina, diverse stochastic global optimization techniques, including genetic algorithms, simulated annealing, and particle swarm optimization, were employed. The active site cavity was carefully chosen, followed by postdocking steps involving energy minimization and H-bond optimization.

Upon thorough docking simulations, we identified 10 compounds that exhibited notably favorable binding energies, suggesting strong interactions with the receptor (►**Table 1**). The binding energy calculated for the top

Table 1 List of potential compounds identified through structure-based virtual screening

Compound ID	Binding energy (kcal/mol)	Interacting residues
LC_87763	−8.346	Thr5, Arg412
LC_33378	−7.858	Thr5, Arg412
LC_27122	−7.409	Thr5, Leu414, Ser441
Enamine_101102	−7.359	Thr5, Gly6, Gly411, Leu414
LC_87632	−7.221	Thr5, Arg412
Enamine_95473	−6.729	Thr5, Leu414
Enamine_68284	−6.489	Thr5, Gly6, Gly411
LC_48628	−6.385	Thr5, Leu414
LC_12121	−6.337	Thr5, Gly411
LC_34889	−6.296	Thr5

compounds ranged from −8.346 to −6.296 kcal/mol. The interacting residues were Thr5, Arg412, Leu414, and Ser441 with the docked ligands (►**Fig. 1**). These compounds demonstrated specific amino acid interactions within the binding site or active site of the receptor, reinforcing the potential for selective binding and biological activity. The identification of these 10 compounds with both promising binding energy and significant interactions with the receptor represents a significant outcome of our study.

From the results we observe, most of the potential compounds were identified from the LifeChemicals database. Out of the 10 compounds, 7 from LifeChemicals and 3 are from the Enamine database. The identified compounds were found to have hydrogen bond, salt-bridge, and pi–pi interactions.

Protein Functional Partners

The comprehensive analysis of functional partners using STRING, KEGG, and REACTOME has yielded crucial insights

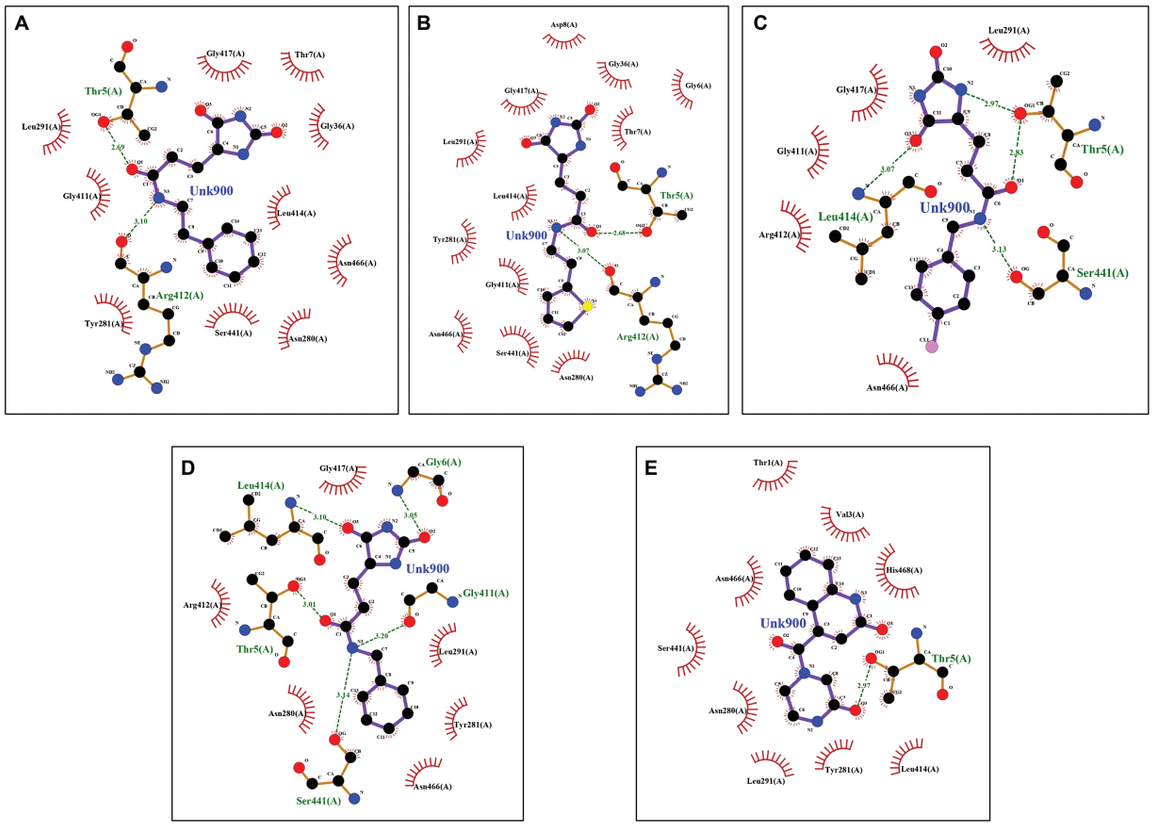

Fig. 1 Two-dimensional interaction diagram of the top five compounds in the active site of the protein. (**A**) LC_87763; (**B**) LC_33378; (**C**) LC_27122; (**D**) Enamine_101102; and (**E**) LC_87632.

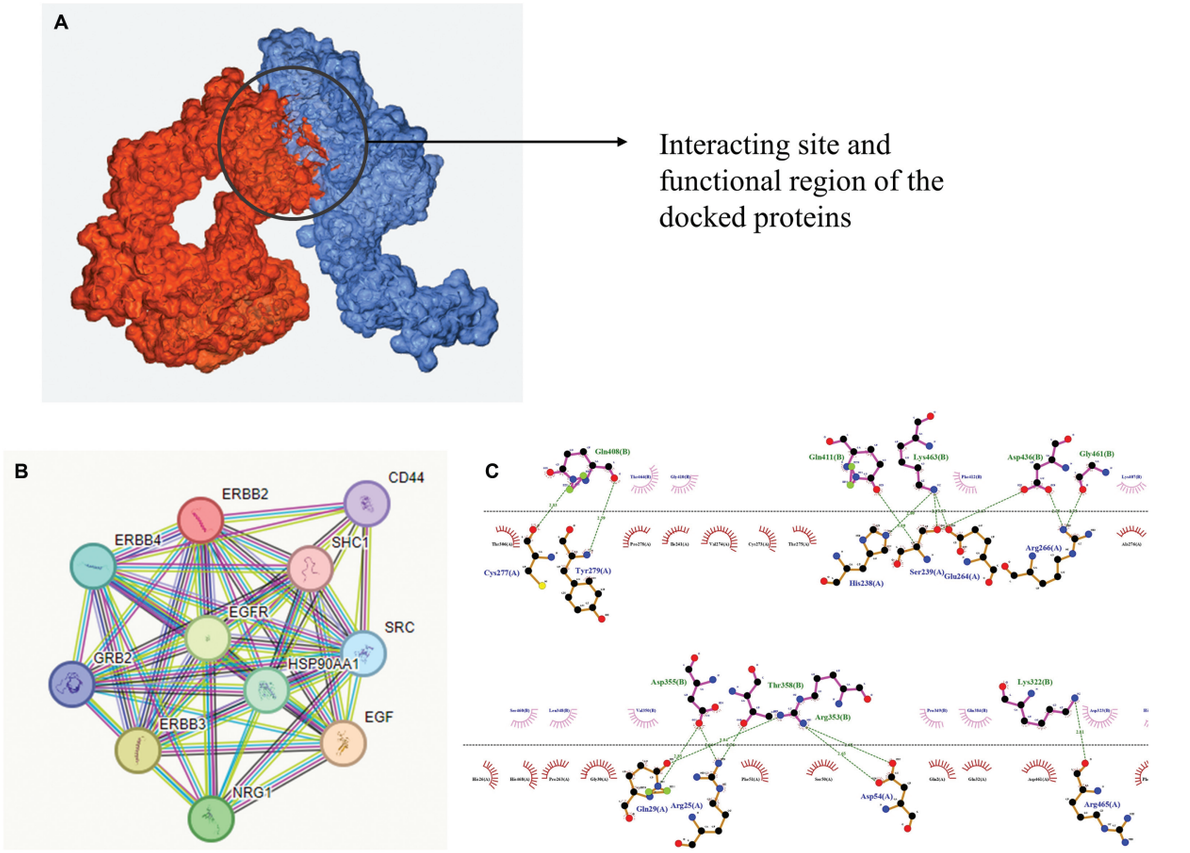

Fig. 2 (A) Protein–protein docking interaction and molecule binding pose representing the interaction site. (B) Interacting amino acid residues from chain A (ERBB2) and chain B (epidermal growth factor receptor).

into the intricate network of interactions involving the ERBB2 protein. Through STRING, we uncovered a multitude of potential interaction partners, which were further enriched and contextualized within biological pathways and processes using the KEGG and REACTOME databases. The rigorous exploration highlighted a significant finding: among the various candidates, epidermal growth factor receptor (EGFR) emerged as the most prominent and compelling functional partner for the ERBB2 protein (►**Fig. 2**). This outcome was supported by multiple lines of evidence, including high-confidence protein–protein interaction scores, shared pathways, and known biological relevance. The identification of EGFR as the best functional partner of ERBB2 underscores its central role in cellular signaling and its potential significance in various physiological and pathological contexts. Further experimental validation and functional studies will be crucial to decipher the specific mechanisms through which this interaction contributes to cellular processes and disease pathways, potentially opening new avenues for therapeutic interventions targeting the ERBB2–EGFR complex.

Protein–Protein Docking

The protein–protein docking studies conducted using HADDOCK 4.2 server provided critical insights into the binding interactions between ERBB2 as the receptor protein and EGFR as the ligand. The docking simulations yielded a range of potential binding modes, allowing us to explore the diverse conformations in which these two proteins may interact. Through comprehensive analysis, we identified a highly favorable binding mode that demonstrated strong binding energy, indicative of stable and specific interactions between ERBB2 and EGFR (►**Table 2**). The best cluster is observed as Cluster 1 with a Haddock score of –95.3, lowest root mean square deviation (RMSD) of 0.6 Å, –384 kcal/mol of Electrostatic energy, and –95.9 kcal/mol of Van der Walls energy. The structure selected from the initial cluster exhibits a Haddock score of –91.46, a minimal RMSD of 0.4 Å, and recorded energy values of –311 kcal/mol for Electrostatic forces and –90.2 kcal/mol for Van der Waals interactions. The important residues of EGFR found in/around the active site comprises nearly 30 amino acids from 353 to 359 and 448 to 464; specifically, Gln408, Lys463, Phe412, and Asp436 are vital residues. The detailed examination of the docked complex revealed key amino acid residues involved in the binding interface, highlighting the precise molecular interactions contributing to the formation of the ERBB2–EGFR complex (►**Fig. 2**). These findings shed light on the potential functional implications of this protein–protein interaction, further underscoring the significance of the ERBB2–EGFR interaction in cellular signaling pathways and disease contexts.

Table 2 Haddock score for the docked complex of ERBB2 and EGFR of Cluster 1

Parameters	Values
Cluster size	53
Haddock score	-95.3 ± 12.5
Van der Waals energy	-95.9 ± 5.1
Electrostatic energy	-384.2 ± 42.6
RMSD from the overall lowest-energy structure	0.6 ± 0.4
Desolvation energy	0.0 ± 3.3
Restraints violation energy	774.2 ± 27.8
Buried surface area	$3{,}259.9 \pm 151.7$
Z-score	–2.1

Abbreviations: EGFR, epidermal growth factor receptor; ERBB2, —; MSD, root mean square deviation.

Toxicity Prediction

The toxicity analysis of the 10 compounds performed using the ProTox-II server has yielded encouraging results. The comprehensive evaluation encompassing multiple toxicity endpoints has revealed that the majority of the compounds demonstrated favorable profiles with no indication of significant toxicity concerns (►**Table 3**). Remarkably, 6 out of the 10 compounds exhibited excellent prediction scores, indicating their potential safety in terms of the assessed toxicity endpoints. It is worth noting that, while the majority of compounds were in an acceptable stage in terms of predicted toxicity, four compounds did exhibit relatively lower prediction scores, suggesting the need for cautious consideration or further assessment before advancing them for experimental testing.

Discussion

Virtual screening's ability to expedite lead discovery, optimize resources, and streamline the drug development pipeline underscores its vital role in modern pharmaceutical research, offering a critical bridge between computational analysis and experimental validation, ultimately driving the development of innovative therapeutic agents that hold the potential to address unmet medical needs and improve patient outcomes. Recently, a study investigated similar workflow using Zinc database with 300 natural compounds. The successful docking of ERBB2 and EGFR using HADDOCK 4.2 demonstrates the utility of this computational tool in deciphering protein–protein interactions, paving the way for future experimental validation and the design of targeted interventions aimed at modulating this critical interaction for therapeutic purposes. These results underscore the importance of such computational toxicity analysis in early stage drug discovery, enabling the identification of compounds with favorable safety profiles and highlighting those that may require additional scrutiny. Further validation through in vitro and in vivo toxicity studies is essential to confirm these predictions and refine our understanding

Table 3 Toxicity prediction of the identified compounds using ProTox-II server

Compounds	Predicted toxicity class	Prediction accuracy	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
LC_87763	CLS 4	92.0%	INACT	INACT	INACT	INACT	INACT
LC_33378	CLS 5	100%	INACT	INACT	INACT	INACT	INACT
LC_27122	CLS 4	88.54%	INACT	INACT	INACT	INACT	INACT
Enamine_101102	CLS 6	63.70%	INACT	INACT	INACT	INACT	INACT
LC_87632	CLS 5	70.97%	INACT	INACT	INACT	INACT	INACT
Enamine_95473	CLS 5	77.80%	ACT	INACT	INACT	INACT	INACT
Enamine_68284	CLS 4	100%	INACT	INACT	INACT	INACT	INACT
LC_48628	CLS 6	92.98%	INACT	INACT	INACT	INACT	INACT
LC_12129	CLS 4	71.90%	ACT	INACT	INACT	INACT	INACT
LC_34889	CLS 5	98.67%	INACT	INACT	INACT	INACT	INACT

Abbreviations: ACT, active; CLS, class; INACT, inactive.

of the overall safety profile of the identified compounds. Nonetheless, the majority of the compounds showing promising results in the ProTox-II analysis represent encouraging candidates for further investigation in drug development efforts.

Conclusion

The results obtained from the combination of various bioinformatics tools and computational methodologies in our study provide a comprehensive understanding of the molecular interactions, binding affinities, functional partnerships, and toxicity profiles of the identified lead compounds. Through protein–protein docking studies utilizing HADDOCK 4.2, we elucidated the binding modes between ERBB2 and EGFR, shedding light on potential interaction mechanisms crucial for cellular processes. Our analysis of functional partners using STRING, KEGG, and REACTOME revealed the pivotal role of EGFR as a functional partner of ERBB2, enhancing our understanding of their interplay in biological pathways. The subsequent toxicity prediction using ProTox-II enabled the early assessment of potential safety concerns, and the identification of compounds demonstrating acceptable toxicity profiles highlights the importance of computational tools in prioritizing lead compounds for further experimental validation. This integrated approach, encompassing molecular docking, pathway analysis, and toxicity assessment, serves as a robust framework for efficient and informed decision-making in drug discovery, accelerating the identification and development of promising candidates while minimizing the risk of adverse effects in the later stages of drug development.

Funding
None.

Conflict of Interest
None declared.

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^{131}I-mIBG Therapy in the Management of High-Risk Neuroblastoma: A Retrospective Study from a Tertiary Level Hospital in South India

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Ind J Med Paediatr Oncol 2025;46:71–76.

Abstract

Introduction Neuroblastoma is the most common extracranial solid tumor in childhood. The data on the treatment experience with ^{131}iodine-meta-iodo-benzyl-guanidine (^{131}I-mIBG) and clinical outcome data are meager from India.

Objectives This article studies the efficacy and treatment outcomes in patients treated with ^{131}I-mIBG in high-risk neuroblastoma.

Materials and Methods The study group consisted of 201 consecutive patients (aged between 1 and 15 years) with biopsy-proven neuroblastoma who underwent ^{131}I-mIBG scans from 2012 to 2022. The majority of these children had a disease that was inoperable or had poor response to chemotherapy. Patients with positive scintigraphy were considered for therapy with ^{131}I-mIBG. The findings were analyzed and correlated with the final diagnosis and outcomes obtained from survival during follow-up and reviewing patient records.

Results Thirty-nine children, 22 males and 17 females, with a median age of 4 years had positive ^{131}I-mIBG scintigraphy. Intra-abdominal primary lesions and osseous lesions were the most common sites of uptake on ^{131}I-mIBG scan. Of these, 13 had upfront chemotherapy and 26 had surgery followed by chemotherapy. All the patients underwent therapy with ^{131}I-mIBG. Fourteen patients had multiple therapies while the remaining 25 had only one therapy. Eight patients had no follow-up, and 13 had disease relapse. The remaining 18 had regression of disease which was confirmed by follow-up ^{131}I-mIBG scintigraphy and with bone scintigraphy in patients with osseous metastases.

Conclusion ^{131}I-mIBG scintigraphy should be preferred in intermediate and high-risk neuroblastoma to know the extent of the disease and also for patient selection for early therapy with ^{131}I-mIBG. It holds significant utility in the management of metastatic neuroblastoma, facilitating palliative pain relief and tumor size reduction in inoperable or metastatic disease.

Keywords
- neuroblastoma
- ^{131}I-mIBG
- ^{131}I-mIBG therapy

article published online
July 18, 2024

DOI https://doi.org/10.1055/s-0044-1787303.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Key Messages

High-risk neuroblastoma can be treated upfront with ^{131}I-mIBG and used in advanced stages to improve overall survival.

Introduction

Neuroblastoma is the most common extracranial solid tumor of childhood which arises from neural crest cells that form the adrenal medulla and sympathetic ganglia.

About 50% of patients at diagnosis[1] present with metastasis most commonly to bone or marrow. Important prognostic factors are age at presentation, histological features, tumor ploidy, N-MYC gene amplification, and stage of the disease, which is based on the International Neuroblastoma Staging System (INSS).[2] The worst outcomes are noted in high-risk diseases defined as stage III or IV in children aged more than 18 months at diagnosis as well as those with N-MYC amplification.

The standard of care for high-risk neuroblastoma includes chemotherapy, surgery, myeloablative therapy, and radiation therapy followed by differentiation therapy using cis-retinoic acid. Despite this multimodality treatment, the outcome is poor[3] with overall survival (OS) ranging from 10 to 60%. Immunotherapy using anti-GD2 antibodies has improved outcomes considerably in high-resource countries; however, this modality is currently prohibitively expensive and hence unavailable to the rest of the world. Iodine 131 meta-iodo-benzyl-guanidine (^{131}I-mIBG) is one of the multimodality treatments that is used mainly in advanced stages of neuroblastoma.[4] Treatment of these high-risk neuroblastoma is essential as this may help in planning the management of the disease.

The current study aimed to analyze the treatment outcomes and to look at the feasibility of this form of treatment as a future therapeutic option in this select group of patients from a tertiary care center in India.

Materials and Methods

Inclusion and Exclusion Criteria

Children aged 1 to 15 years, diagnosed to have high-risk neuroblastoma from 2012 to 2022 who had a positive ^{131}I-mIBG scintigraphy were included in this study. Diagnosis of neuroblastoma was confirmed by a biopsy of either the primary tumor or bone marrow (BM) trephine and supported by elevated urine catecholamines. The disease was staged according to the revised INSS and the assessment of response was according to the International Neuroblastoma Response Criteria.[2] ^{131}I-mIBG scintigraphy was done in 201 patients for metastatic workup, among which 168 patients had shown positive uptake. Thirty-nine patients among them who had a positive mIBG scintigraphy during the period of the study received treatment with ^{131}I-mIBG for metastatic or inoperable disease or relapse of the disease after standard care based on decisions by the multidisciplinary tumor board that included pediatric oncologists, surgeons, radiation oncologists, and nuclear medicine physicians.

^{131}I-mIBG Imaging

^{131}I-mIBG which was prepared in-house using carrier-free ^{131}iodine was used[5] to assess for mIBG uptake. A dose of 0.5 mCi was administered intravenously and whole-body planar images were acquired using a gamma camera (Infinia Hawkeye, GE Healthcare, Milwaukee, Wisconsin, United States) at 24, 48, and 72 hours postinjection. Anterior and posterior whole-body images were acquired with a window centered at 364 keV $\pm$ 15 and a matrix of 256 $\times$ 1024 for 450 s/step in three steps. Single-photon emission computed tomography (CT)/ low-dose CT was acquired for doubtful lesions and anatomical localization.[6]

Posttherapy ^{131}I- mIBG whole-body scintigraphy in anterior and posterior projections was done on the third day after the therapy to look for any lesions not seen on the diagnostic pretherapy scans[7] and also confirm the uptake of mIBG in the target lesions.

^{131}I-mIBG Therapy

Patients were treated in a room specially designed for radioisotope therapy. ^{131}I-mIBG was administered as slow infusion intravenously over 3 to 4 hours with hydration.

Thyroid gland blockade was provided with potassium perchlorate by oral administration from 2 days before therapy to 5 days posttherapy. Blood pressure and heart rate were monitored during the procedure and for 24 hours after treatment. There was no adverse reaction during or shortly after the administration of ^{131}I-mIBG therapy for any of the patients. Dosage was given according to a weight-based regimen with a dose of 37 to 74 MBq/kg (1–2 mCi/kg) to all the patients and patients were discharged once the levels of exposure were $<$ 50 micro-Sv at a 1-m distance which conferred to the Atomic Energy Regulatory Board, India standard guidelines.

Primary Outcome

Patients who were treated with ^{131}I-mIBG were followed up after 6 months to look for response evaluation. ^{131}I-mIBG scintigraphy and urinary catecholamine levels were done. Progression of the disease was considered when there was an increase in the intensity of ^{131}I-mIBG uptake or any new lesions noted compared with the posttherapy scan and increase in urinary catecholamine levels (►**Fig. 1**). Partial regression of the disease was considered when there was a decrease in the number of lesions or intensity of lesions and decrease in the levels of urinary catecholamine (►**Fig. 2**).

Statistical Analysis

Categorical data were summarized using percentages. Numerical data were summarized as the means and standard deviations or medians and ranges. Due to the small sample size multivariable Cox regression for determining independent predictors of survival was not possible.

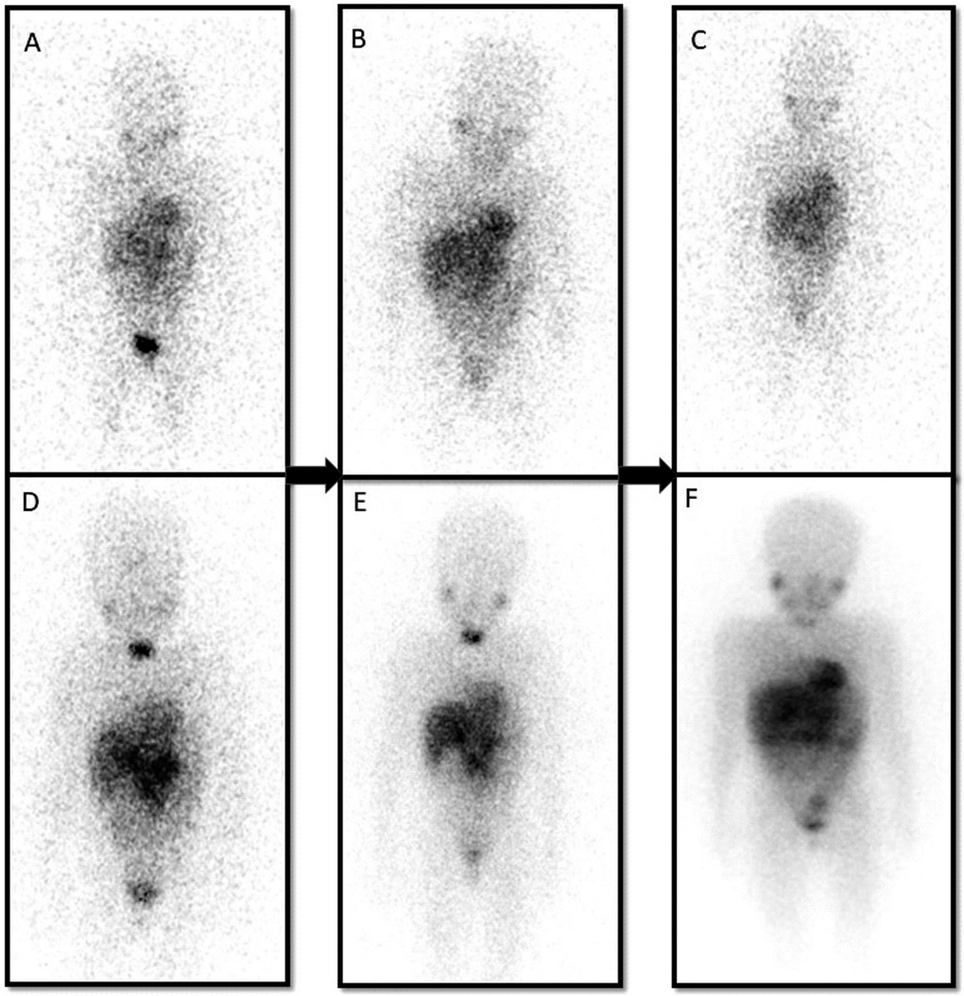

Fig. 1 A 6-year-old child with a primary lesion in the mediastinum (**A**). Progression of the disease as the areas of uptake have increased despite two ^{131}iodine-meta-iodo-benzyl-guanidine (^{131}I-mIBG) therapies on the posttherapy scans (**B**).

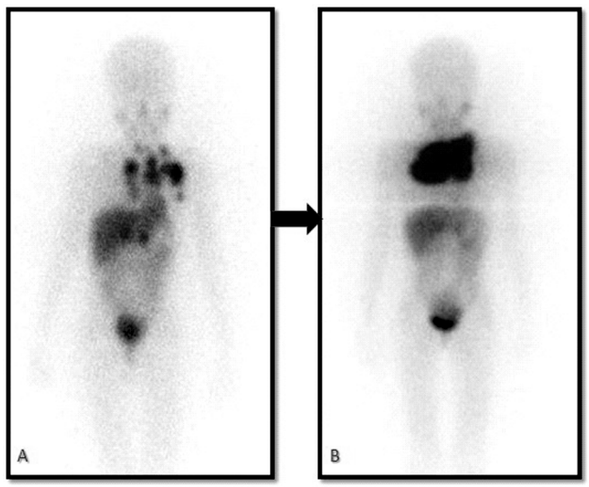

Fig. 2 A 7-year-old child with a primary abdomen lesion and multiple osseous metastases in the pretherapy scan (**A–C**). Partial regression is noted as the areas of uptake have significantly reduced after three ^{131}iodine-meta-iodo-benzyl-guanidine (^{131}I-mIBG) therapy as seen in the posttherapy images (**D–F**).

Ethical Approval Statement

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Ethics Committee Approval was obtained from the Institutional Ethics Committee vide letter no. IRB Min No. 15495 (RETRO) dated June 28, 2023.

Results

Results

Thirty-nine of 201 children who had a positive ^{131}I-mIBG scan received ^{131}I-mIBG therapy. There were 22 boys and 17 girls with their ages ranging from 1 to 15 years with a median age of 4 years. Six children had stage III disease and all the rest had stage IV neuroblastoma. Twenty-four children received COJEC (cisplatin [C], vincristine [O], carboplatin [J], etoposide [E], and cyclophosphamide [C]) chemotherapy, 7 had carboplatin-etoposide/CADO (cyclophosphamide, doxorubicin, and vincristine), and the rest of the children who had chemotherapy elsewhere prior to coming to our hospital had

Table 1 Patient characteristics

Total no. of patients	39
Male	22
Female	17
Age at diagnosis	
Range	1–15
Mean	5.9
Median	4
Histopathology	
Neuroblastoma	35
Ganglioneuroblastoma	4
Immunohistochemistry	
Synaptophysin, chromogranin, and NSE	35 of 39 (4 were operated elsewhere)
Stage of the disease	
Stage 3	7
Stage 4	32
Presentation	
Inoperable primary	20
Skeletal metastasis	13
Primary with skeletal metastasis	3
Extraosseous metastasis	3
Treatments prior to ^{131}I-mIBG therapy	
Chemotherapy followed by	
Debulking surgery	28
Chemotherapy	11
^{131}I-mIBG therapies	57
1 dose	25
2 doses	10
3 doses	4
^{131}I-mIBG activity (mCi)	37–74 MBq/kg body weight
	1–2 mCi/kg body weight
Follow-up	
Period	12–60 mo
Mean	25 mo
Results based on posttherapy ^{131}I-mIBG scan	
Regression	18
Progression	12
Lost to follow-up	9
Post ^{131}I-mIBG treatment in progressive disease	
Chemotherapy	7
Radiation therapy	1
Supportive/palliative treatment	4

Abbreviations: ^{131}I-mIBG, ^{131}iodine-meta-iodo-benzyl-guanidine; NSE, neuron-specific enolase.

OPEC (vincristine, prednisolone, etoposide, and chlorambucil)-based chemotherapy. The baseline characteristics of the cohort are shown in ►**Table 1**.

The location of the primary tumor was suprarenal in 10, retroperitoneal in 9, paraspinal in 4, thorax/neck in 4, and undetected primary with extensive bone and/or BM disease in 12 children. ^{131}I-mIBG scan just prior to ^{131}I-mIBG therapy showed uptake in multiple bones in 12 children, at primary site in 24 children, and 3 children with both primary and bone lesions. Indications for ^{131}I-mIBG therapy included metastatic disease, refractory to standard therapy in 13, relapse/recurrence of disease in 9 (2 post-myeloablative therapy relapse), and inoperable primary with or without metastasis in 17. ^{131}I-mIBG therapy was given with a curative intent for 6 children and in the remaining 33 it was given with palliative intent. Twenty-five patients had received a single dose of ^{131}I-mIBG therapy.

For patients who had positive ^{131}I-mIBG scintigraphy in the follow-up scan done 6 months after the first therapy underwent further doses of ^{131}I-mIBG therapy, two doses were given for 10 patients and three doses for 4 patients.

Eighteen patients (46%) had partial regression of the disease identified by follow-up ^{131}I-mIBG scintigraphy and catecholamine levels, 12 patients (30%) had progression of the disease, and 9 patients had been lost to follow-up. The median follow-up was 21 months (range: 10–60 months). They were also regularly followed up with complete blood count profile to look for any thrombocytopenia and neutropenia which are the most common side effects of ^{131}I-mIBG therapy. Among the 30 children who were followed up, 18 patients had a regression and were doing well on the last follow-up. Among the 12 patients who had progression of the disease, irinotecan and isotretinoin acid-based chemotherapy and radiation therapy were given to 7 children and the remaining 5 children succumbed to the disease during the follow-up.

Discussion

High-risk neuroblastoma is most often associated with poor OS and mostly presents with metastases at initial presentation.[1] Current imaging guidelines for staging neuroblastoma are based on the INSS which recommends CT/magnetic resonance imaging for primary disease and ^{131}I-mIBG for metastatic disease.

Although ^{123}I-mIBG is recommended, due to unavailability in the Indian setting, ^{131}I-mIBG is used for pretherapy workup and subsequent therapy. Our study included 201 patients diagnosed with neuroblastoma who underwent ^{131}I-mIBG scintigraphy as it is useful for documentation of primary and metastatic lesions and also to assess response to therapy, whereas 18F-fluorodeoxyglucose positron emission tomography (PET)/CT has only a complementary role for response assessment.[8] Among them 39 patients with positive ^{131}I-mIBG scintigraphy were referred for therapy with ^{131}I-mIBG.

Long-term survival of children with inoperable or disseminated neuroblastoma diagnosed after 1 year of age remains largely unsatisfactory. This may be attributed to the fact that current treatment commonly fails to completely eradicate the disease. It is also noted that 70% of remission rates are achieved by surgical resection, chemotherapeutic agents, and radiation therapy. Despite these treatments, there are high chances of relapse rate,[9] possibly due to the aggressive nature of the disease.

Approximately 75% of neuroblastomas have ^{131}I-mIBG uptake[10] which makes it an effective therapeutic agent and can be used for treatment upfront as in our study. ^{131}I-mIBG has proven to be useful for inoperable tumors, to improve overall disease-free survival rates, and reduce bone pain. Irrespective of some success, ^{131}I-mIBG systemic therapy is still not the mainstay of treatment. ^{131}I-mIBG therapy dosage used in neuroblastoma varies among different centers and is used in low and high doses. In our study, we had used doses ranging from 1 to 2 mCi/kg which can be used to achieve a response in the form of palliative pain reduction. This low dose does not require the use of a subsequent stem cell transplantation as it is associated with lower hematological toxicity compared with a high-dose regimen. ^{131}I-mIBG were given at a high dose ranging from 12 to 20 mCi/kg body weight,[11] which are mainly administered as a myeloablative dose before stem cell transplantation without many complications as seen in various studies.

Most of the patients in our study had upfront treatment with either chemotherapy (26/39, 66%) or surgery (11/39, 28%), except for two patients who presented with an inoperable primary and were given upfront ^{131}I-mIBG as induction therapy.[12] All of the patients presented with advanced-stage disease with bone and BM metastasis corresponding to high-risk neuroblastoma.[1] Various studies suggested a time interval of 2 to 6 months between treatment sessions and in our study, the interval was 6 months.[13] Though various objective response scales like the Curie scale[14] are available to look for treatment response, it was not used in our study partly as it was a retrospective study and few were lost to follow-up.

Only a few minor side effects were observed during the ^{131}I-mIBG infusion and 3 to 4 days posttherapy, some patients complained of temporary nausea and vomiting.

Various studies have demonstrated that these side effects can be managed symptomatically with antiemetics.[15] No serious acute side effects, such as hypertensive encephalopathy, accelerated hypertension, or death, were seen during therapy. Change in thyroid function was not observed in the follow-up patients as there was an adequate pretherapy blockade of the thyroid with perchlorate, although there is long-term thyroid complication reported in patients treated with ^{131}I-mIBG.[16]

Patients who were lost to follow-up were mainly due to bleak prognosis and the moribund state as there was a lack of effective salvage treatment.[17]

We have outlined our experience in a tertiary care hospital in South India in treating high-risk neuroblastoma with ^{131}I-mIBG therapy. Among those treated, 18 (46%) patients were found to have partial regression of the disease which is in comparison to other studies,[18] though cannot be an independent predictor of OS.[11] Johnson et al also demonstrated similar outcomes which favored the use of ^{131}I-mIBG

therapy in the standard-of-care treatment of high-risk neuroblastoma with multiple and subsequent doses.[19]

Future Directions

This study and other contemporary studies indicate that ^{131}I-mIBG therapy can achieve a significant reduction in disease burden and pain in high-risk neuroblastoma patients. With the development of new radiotracers in the form of fluorinated form of mIBG, 18F-meta-fluorobenzylguanidine to detect lesions using PET[20] with improved lesion detection, the utility of ^{131}I-mIBG therapy is going to become included in the management of neuroblastoma.

Limitations

Our study had limitations which included the retrospective nature of the study from a single institution and the small sample size. In addition, a standardized protocol for dosimetry of the ^{131}I-mIBG therapy is not available.

Conclusion

^{131}I-mIBG scintigraphy serves as a crucial tool for disease staging and patient stratification for ^{131}I-mIBG therapy. It holds significant utility in the management of metastatic neuroblastoma, facilitating tumor size reduction, particularly in cases where surgical interventions or initial chemotherapy and radiation treatments have proven ineffective.

Note

The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Patient Consent

Waiver of consent form obtained as it's a retrospective study.

Conflict of Interest

None declared.

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Clinical Profile of Febrile Neutropenia in Children with Malignancies in a Tertiary Care Hospital: A Prospective Observational Study

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Ind J Med Paediatr Oncol 2025;46:77–86.

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Abstract

Introduction Febrile neutropenia is a dreadful complication associated with malignancies. Knowledge of locally prevalent pathogens and their resistance pattern is of paramount importance in guiding antimicrobial therapy.

Objectives The aim of the study was to identify the common infectious agent, antibiotic susceptibility of culture positive patients, and outcome

Materials and Methods We conducted a single-center prospective observational study. Forty-three children with febrile neutropenia episodes admitted in KKCTH, Chennai, were included in the study. The duration of the study was 1 year. Relevant patient and disease specific details were obtained, results were analyzed, and conclusions were drawn.

Results There were 90 episodes of febrile neutropenia. Overall culture positivity was identified in 37 cases (41.11%). Bacteremia (23.3%) was the most common cause of microbiologically documented infection. Gram-positive organisms (60%) were more commonly documented. Among the gram-positive organisms, coagulase-negative *Staphylococcus aureus* was the predominant isolate followed by *Streptococcus*. Central line–associated bloodstream infections were documented in 13.33%. Chemo-port removal was done in four children. Three had invasive fungal disease. The majority of the gram-negative isolates were resistant strains. Morbidity was significantly more in gram-negative infections. Overall outcome was good though three children succumbed to sepsis.

Conclusion A vigilant management of illness is essential. Chemo-port carries risk of severe infection. Protocol-based management of catheter-related bloodstream infection (CRBSI) can limit the number of chemo-port removal. Though gram-positive organisms are in the rise, gram-negative organisms are still responsible for significant morbidity. Early initiation of broad-spectrum empirical antibiotics with optimal gram-positive coverage is crucial. Children with suspected fungal infections should be aggressively evaluated and treated. An organized approach is the key in successful management.

Keywords
- acute lymphoblastic leukemia
- CRBSI
- microbiologically documented infection
- invasive fungal disease
- gram-negative organism

article published online
August 5, 2024

DOI https://doi.org/10.1055/s-0044-1788702.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Key Messages: Initiation of broad-spectrum antibiotics at the earliest during an episode of febrile neutropenia is the determinant factor of the outcome.

Introduction

The advancements in cancer care have led to better cure rates for patients suffering from various malignancies, while at the same time making them susceptible to complications of therapy. Febrile neutropenia is one such complication and one of the most common admitting *diagnoses* among *pediatric* oncology units, second only to admissions for chemotherapy.[1] A delay in appropriate management is associated with higher morbidity, mortality, a prolonged duration of hospital stay, and higher costs of treatment.[2] The strategy of using empirical antibiotics has led to a considerable decline in infection-related mortalities. Knowledge of the locally prevalent pathogens and their resistance pattern is of paramount importance in guiding antimicrobial therapy. There have been very few Indian studies looking at this changing trend of microbiome in the *pediatric population*. Our aims and objectives of this study are to identify the common infectious agent associated with febrile neutropenia, antibiotic susceptibility pattern, and outcomes.

Materials and Methods

It is a prospective observational study. The duration of study is 1 year (January 2019–January 2020).

Inclusion criteria:

- Febrile neutropenia episodes in children aged less than 18 years, with an underlying malignancy.

Exclusion criteria:

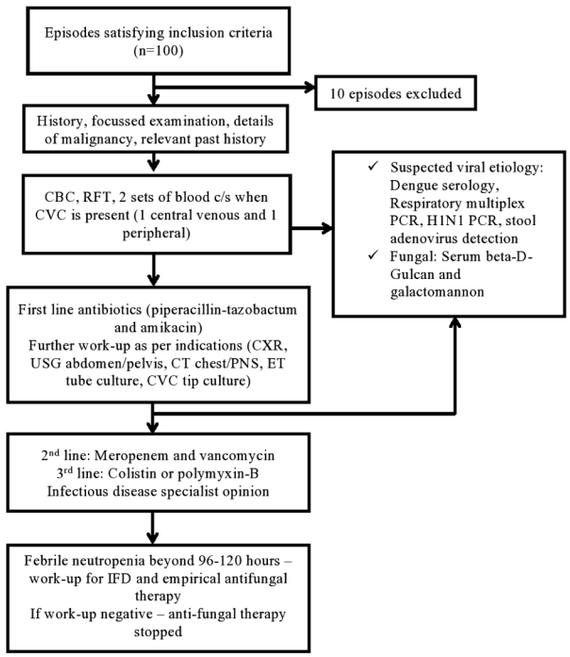
- Children who have undergone hematopoietic stem cell transplantation.
- Episodes that were pretreated elsewhere.
- Children who have a preexisting inborn error of immunity.
- Parents who refused to be a part of the final sample size of the study: 90 episodes.

Methodology

Each episode of febrile neutropenia was considered an individual event, with comprehensive bedside histories obtained to gather pertinent information regarding both the underlying malignancy and febrile illness. Detailed clinical examinations were conducted to identify potential sources of infection, and baseline investigations upon admission encompassed a complete blood count (CBC), renal function tests, and blood cultures obtained through aseptic techniques. Analysis of the culture reports focused on organism identification and antibiotic sensitivity patterns. Secondary investigations were performed based on suspected sources of infection, including urine analysis/culture, chest X-ray imaging, and abdominal ultrasonography. Patients with suspected viral etiology underwent serology tests such as respiratory biofire panel (multiplex polymerase chain reaction [PCR]), dengue NS1 antigen and immunoglobulin M (IgM)/IgG antibody *titers*, H1N1 PCR testing, or stool adenovirus detection. Those with suspected fungal etiology underwent serum galactomannan and serum beta-D-glucan level assessments, along with computed tomography (CT) scans of the chest and/or paranasal sinus to pinpoint the focus of infection (►**Fig. 1**).

Treatment initiation followed our institutional protocol. Children diagnosed with febrile neutropenia received empirical antibiotic therapy consisting of piperacillin-tazobactam and amikacin, as directed by our institutional antibiogram. Blood cultures were collected before initiating the antibiotics. After 48 hours, in the absence of microbial growth in the cultures, amikacin was discontinued. Piperacillin-tazobactam was continued until the final culture report, provided the child exhibited clinical improvement. In cases of clinical deterioration, antibiotic escalation to second-line agents was implemented. Beyond 96 to 120 hours of febrile neutropenia, empirical antifungal therapy was commenced. High-risk individuals for invasive fungal disease (IFD) received liposomal amphotericin-B, with concomitant workup for fungal infection. Conversely, preemptive antifungal treatment with azoles or liposomal amphotericin-B was implemented in low-risk patients. All children received cotrimoxazole for *Pneumocystis jiroveci* prophylaxis. Additionally, those at high risk of invasive fungal disease received either fluconazole or voriconazole prophylaxis, based on susceptibility to yeast or molds, respectively.

Monitoring included assessing antibiotic effectiveness and escalating treatment as necessary, with careful documentation of patterns and reasons for escalation. Patients unresponsive to initial antibiotic regimens or exhibiting



CBC = Complete blood count; RFT = Renal function test; c/s = culture/sensitivity; PCR = Polymerase chain reaction; CXR = Chest X-ray imaging; USG = Ultrasonography; CT = Computerised Tomography; PNS = Para-nasal sinuses; ET = Endotracheal tube; CVC = Central venous catheter; IFD = Invasive Fungal Disease

Fig. 1 Methodology flow chart.

Table 1 Definitions and descriptions

Febrile neutropenia	Single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period, with <500 neutrophils/mm^3 or <1,000 neutrophils/mm^3 with a predicted decline to 500/mm^3 over the next 48 h
Clinically documented infections (CDI)	Episodes where a site of infection has been identified either clinically or radiologically and cultures and other pathogen-directed workups are negative
Acute febrile illness not otherwise specified (AFI-NOS)	Episodes of fever where an infection cannot be demonstrated neither clinically nor microbiologically
Microbiologically documented infection (MDI)	Episodes where a pathogen has been identified in microbiological samples
Paired cultures	Cultures drawn from a central venous access and from a peripheral venous access or two different peripheral venous accesses
Catheter-related bloodstream infections (CRBSI)	A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood sample culture and from the catheter tip or that 2 blood samples for culture be obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP)
Possible CRBSI	2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least threefold greater than the colony count for the blood sample obtained from the second lumen
DTP for CRBSI	CRBSI is defined as the growth of microbes from blood drawn from a catheter hub at least 2 h prior to microbial growth being detected in blood samples obtained from a peripheral vein
High-risk conditions for invasive fungal disease	Acute myeloid leukemia, high-risk acute lymphoblastic leukemia, or relapsed acute leukemia; those with prolonged neutropenia; those receiving high-dose steroids; and those undergoing allogeneic HCT in the first year after HCT without evidence of T-cell reconstitution, those or receiving steroids or multiple immune suppressive agents to prevent or treat graft-versus-host disease
Low-risk conditions for invasive fungal disease	Febrile neutropenia, not meeting the criteria of high risk

Abbreviation: HCT, Hematopoietic cell transplantation.

clinical deterioration underwent repeat CBC and blood cultures (aerobic bacterial and fungal). Additional investigations were undertaken for pediatric intensive care unit (PICU) patients, encompassing endotracheal tube cultures for ventilated individuals, central line catheter tip cultures for those with central lines, and urinary catheter tip cultures for patients with Foley catheters (see ►**Table 1** for definitions). Furthermore, all patients needing PICU care underwent rectal swab culture screening for carbapenem-resistant Enterobacterales (CRE). Mortality and morbidity among study participants associated with febrile neutropenia were documented.

Statistical Methods

Statistical analysis was done using SPSS 16.0. Frequency tables and descriptive statistics were calculated for background variables. For data that did not follow normal distribution, nonparametric tests were used. To compare the difference in quantitative variables between two groups, the Mann–Whitney *U* test was used, whereas the Kruskal–Wallis test was used for quantitative variables in more than two groups. Chi-squared tests were employed for comparing the difference in proportions. For data that followed normal distribution, Student's *t*-test and chi-squared test were applied. For the statistical analysis, 95% confidence interval (CI) was used, and a *p*-value of less than 0.05 was considered significant.

Definitions, descriptions, and categories are presented in ►**Tables 1** and **2**.[3–6]

Ethical Approval

This study was approved by the CHILDS Trust Medical Research Foundation ethical committee (ECR/676/Inst/TN/2014/RR – 17).

Table 2 Categories of invasive fungal disease

Category	Definition
Proven	Proof of invasive fungal disease by demonstration of fungal elements in diseased tissue of most conditions
Probable	Host factor, clinical features, and mycological evidence are present
Possible	Host factor and clinical features without mycological evidence

Ethics

The study was approved by the CHILDS Trust Medical Research Foundation (IBR approval number: ECR/676/Inst/TN/2014/RR – 17; date: February 20, 2018).

Helsinki Declaration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

A total of 43 children with 90 febrile neutropenia episodes were enrolled in the study. Majority of the episodes were in preschool children (71%) and had *hematological* malignancy (78%). Among all the hematological malignancies, acute lymphoblastic leukemia (ALL) constituted about 66% of the cases. The risk stratification and management of ALL were implemented in accordance with the Indian Collaborative Childhood Leukemia Group (ICiCLe) study protocol. Among the children with ALL, 34 (57%) episodes made up the intermediate- and high-risk groups, whereas 26 (43%) were standard risk. Intensive chemotherapy preceded 51 (85%) episodes. More than 53% ($n = 48$) episodes did not have a clear focus of infection. The baseline characteristics are outlined in the ►**Table 3**.

All the febrile neutropenia episodes were divided into three categories: microbiologically documented infections (MDIs; 41.1%, $n = 37$), clinically documented infections (17.7%, $n = 16$), and acute febrile illness not otherwise specified (AFI-NOS; 41.1%, $n = 37$; ►**Table 1**).

Severe neutropenia (absolute neutrophil count [ANC] < 500 cells/μL) was encountered in 52.2% of episodes. Sixty-one (67.8%) episodes had neutropenia lasting for less than a week, while 39 (32.2%) episodes had neutropenia lasting for more than a week. Episodes with severe neutropenia also had a significantly prolonged duration of neutropenia, further augmenting the risk of infection, and this was statistically significant ($p = 0.029$). Children with AFI-NOS had a shorter duration of neutropenia. The majority (75.9%, $n = 22$) of episodes, which had neutropenia lasting for more than a week, had MDI. On the other hand, only 25.5% ($n = 15$) had an MDI with neutropenia lasting less than a week. The difference was statistically significant ($p < 0.0001$).

The MDIs were further classified as those with *bacteremia* and those with fungemia. Twenty-one (57%) episodes had *bacteremia* and 1 (2.7%) had candidemia. Paired cultures were found to be positive in 14 (25.9%) cases (►**Fig. 2**). Bronchoalveolar lavage revealed growth of *Candida* spp. (6.6%, $n = 1$) and *Aspergillus* spp. (6.6%, $n = 1$), while endotracheal tube cultures showed the presence of *Escherichia coli* (6.6%, $n = 1$). Pus cultures indicated the presence of methicillin-resistant *Staphylococcus aureus* (MRSA; 26.6%, $n = 4$), and stool cultures yielded CRE *E. coli* (20%, $n = 3$) and *Clostridium difficile* (6.6%, $n = 1$). Additionally, urine cultures exhibited growth of *Klebsiella* spp., CRE *E. coli*, and *Enterococcus* spp. Polymicrobial infections were documented in 6 (28.5%) episodes. All cultures indicated growth within 48 hours of incubation; earliest growth was documented to be within 6 hours. There were in total 14 episodes of suspected IFDs, comprising 3 proven cases, 3 probable cases, and 8 possible cases (►**Table 2**). All the children were receiving cotrimoxazole prophylaxis for *P. jiroveci*, while six children were additionally on fluconazole prophylaxis for yeast, and four were on voriconazole prophylaxis for further protection against molds. None of them had any breakthrough fungal infection.

Workup for viral infection was positive in 6 (16.2%) cases. Of note, 11 (31%) did not have a clear focus. Overall, the

Table 3 Baseline characteristics

Total episodes: 90	Frequency of episodes	Percentage
Age distribution (mean 4.6 ± SD)		
< 5 y	64	71.1
5–10 y	18	20.0
> 10 y	8	8.88
Gender distribution		
Boys	50	55.6
Girls	40	44.4
Nutritional status		
Undernourished	16	17.78
Well nourished	74	82.22
Underlying malignancy		
B-cell ALL	56	62.2
T-cell ALL	4	4.4
AML	11	18.3
NHL	5	5.5
Hodgkin's lymphoma	1	1.11
Peripheral T-cell lymphoma	1	1.11
LCH	1	1.11
Nonhematological malignancy	11	12.2
Site of infection		
No focus	46	53.3
Respiratory tract infection	18	20
Vascular access related	8	8.9
Gastrointestinal tract	5	5.6
Skin and soft-tissue infection	8	8.9
Genitourinary tract	3	3.3

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; LCH, Langerhans cell histiocytosis; NHL, non-Hodgkin's lymphoma; SD, standard deviation.

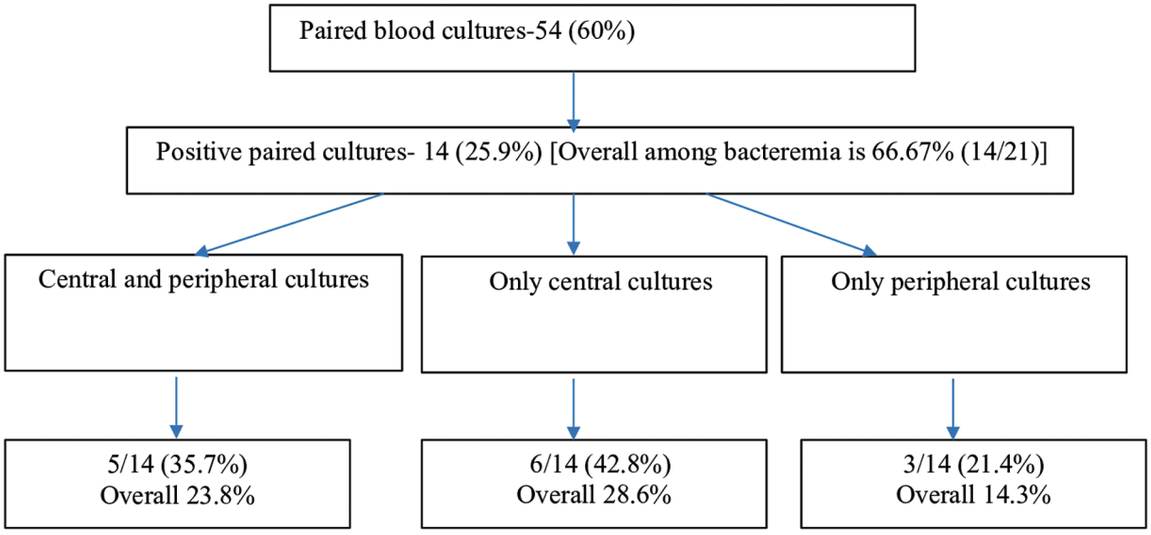


Fig. 2 Paired blood culture positivity.

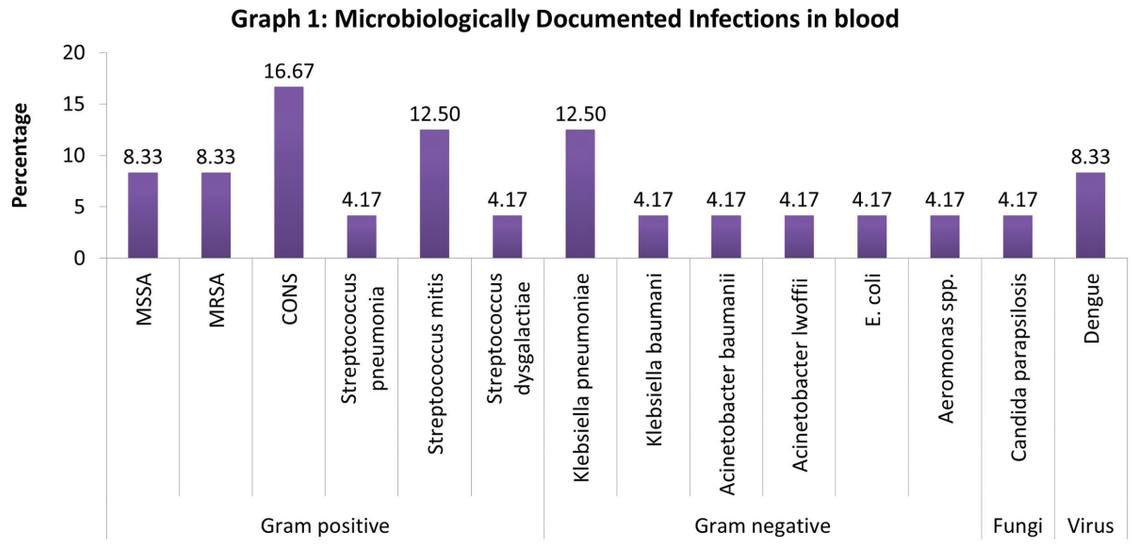


Fig. 3 Clustered column graph depicting spectrum of microbiologically documented infections in blood.

pattern of organisms attained by various laboratory methods in variant body tissues is entailed in the ►**Figs. 3** and **4**.

Catheter-Related Bloodstream Infections

Out of the 21 (23.33%) MDI with bacteremia, 12 (13.33%) were central line–associated bloodstream infections. Nearly 8.9% ($n = 8$) were long-term line (chemo-port) related infections and 4.4% ($n = 4$) were short-term-line-related infections. Multidrug-resistant (MDR) *Klebsiella* spp., MDR *Acinetobacter* spp., *E. coli*, MRSA coagulase-negative *Staphylococcus* (CONS), *Streptococcus mitis*, and *Candida parapsilosis* were the organisms responsible for catheter-related bloodstream infection (CRBSI) in our cohort. Management of CRBSIs was done in accordance with the Infectious Diseases Society of America (IDSA) 2009 guidelines. Four children had to undergo chemo-port removal as a part of source reduction. The antibiotic susceptibility of the pattern of the isolates in our study is shown in the ►**Figs. 5** and **6**.

Treatment

Piperacillin-tazobactam with amikacin was the first-line antibiotic in all episodes with febrile neutropenia. Escalation to second-line antibiotics was done in 31.1% of cases. Both meropenem and vancomycin were used in 21 (71.4%) episodes, 5 (17.8%) cases received only meropenem, and

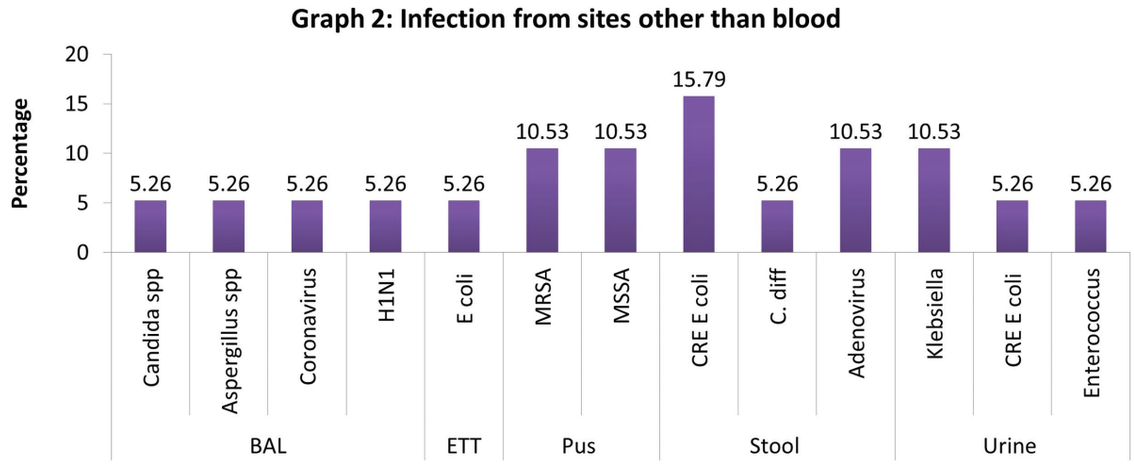


Fig. 4 Clustered column graph depicting spectrum of microbiologically documented infections in sites other than blood.

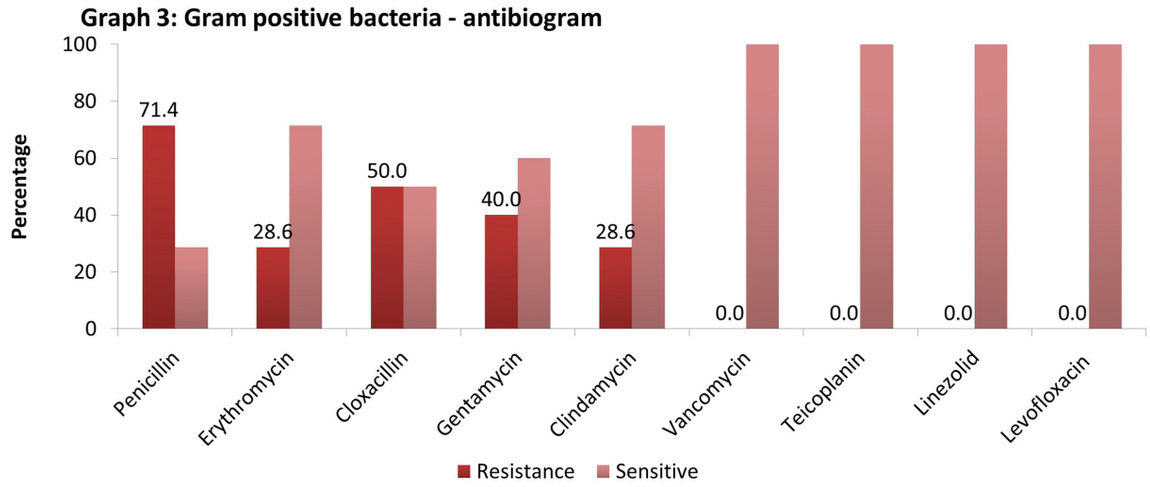


Fig. 5 Clustered column graph depicting the sensitivity pattern of gram positive bacteria.

3 (10.7%) cases received only vancomycin. Further escalation to colistin or polymyxin-B was done in 5 (5.55%) cases.

Seventeen (45.9%) episodes of MDIs required escalation to second-line antibiotics, whereas only 11 (20.8%) without any microbiological proof required further escalation ($p = 0.011$). Mean rank of treatment duration (58.8) and hospital stay (62.73) were also significantly higher whenever escalation of antimicrobial drugs was required ($p = 0.001$). PICU care was often required (35.7%, $n = 10$) during the episodes requiring escalation ($p < 0.0001$). IFD was suspected in 14 (16.6%) episodes and proven in 3 episodes. Empirical antifungals were started in 6 (42.8%) episodes with liposomal amphotericin-B and 8 (57.1%) episodes with azoles.

Granulocyte colony stimulating factor (G-CSF) prophylaxis was provided in 8 (27.5%) cases (with underlying solid *tumors*) and 21 (72.4%) received it as treatment in view of profound prolonged neutropenia.

Intensive care treatment was required in 14 (15.55%) episodes. Inotrope or vasopressor requirement was observed in 4 (28.5%) cases. The need for invasive ventilation was observed in 4 (28.5%) cases. Notably, episodes with MDI (35.1%, $n = 13$) were found to require PICU care more frequently than those without (1.9%, $n = 1$) microbiological diagnosis ($p < 0.0001$). In particular, *gram-negative* sepsis (61.5%, $n = 8$) had a significantly higher requirement of PICU care than gram-positive (16.7%, $n = 3$) sepsis ($p = 0.01$).

Outcome

The median duration of hospital stay was 5.5 days (range: 3–45 days). Episodes with gram-negative sepsis had a substantially prolonged (mean-rank of 20.73 days) hospital course

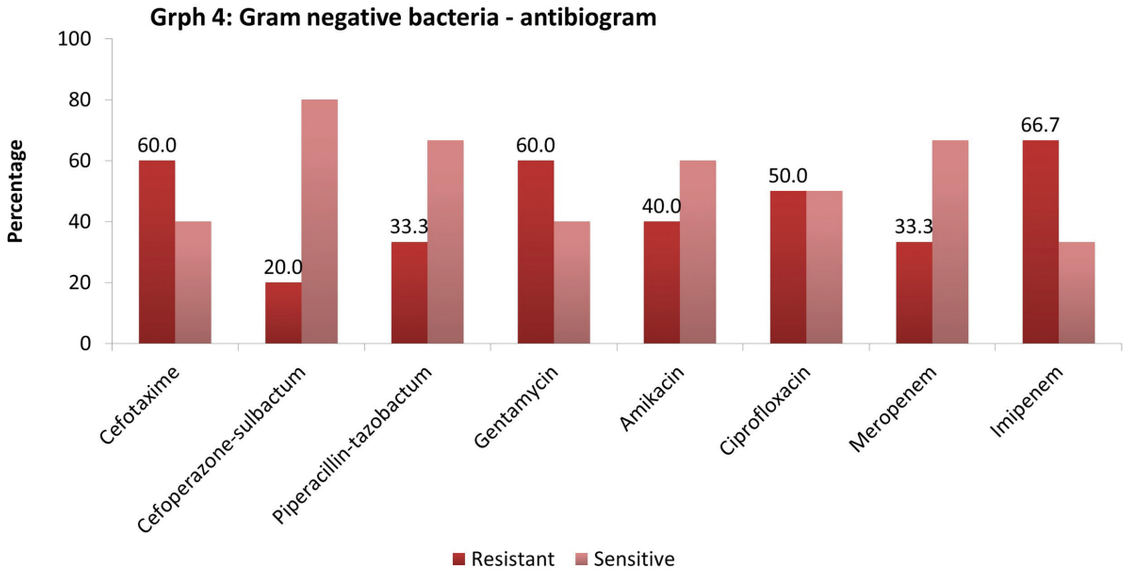


Fig. 6 Clustered column graph depicting the sensitivity pattern of gram negative bacteria.

than gram-positive (mean-rank of 12.58 days) sepsis ($p = 0.013$). Episodes with AFI-NOS had shorter duration of hospital stay than MDIs ($p = 0.001$). Three children (3.33%) succumbed to the illness during their hospital stay. All three children had MDIs: two had gram-negative sepsis and one had dengue.

Discussion

The significance of infectious complications in febrile neutropenia cannot be overstated, as they contribute substantially to morbidity and mortality. A comprehensive understanding of the local patterns of febrile illness is crucial for effective management.

In our study, the majority (71.1%) of febrile neutropenia episodes occurred in children younger than 5 years. Both males and females were affected in nearly equal proportions. Eighty-eight percent of cases were associated with an underlying hematological malignancy, a proportion consistent with findings reported by Babu et al[7] and Soumya and Ajit Kumar.[8] This alignment may be attributed to the elevated prevalence of hematological malignancies in the pediatric population, necessitating more intensive therapeutic interventions and consequently heightening susceptibility to serious infections. Notably, a significant number of febrile neutropenia episodes occurred during the induction phase of chemotherapy, underscoring the vulnerability of patients during this particular treatment stage.[2,9]

The primary imperative is to meticulously gather a focused patient history and promptly initiate appropriate antibiotics following blood culture collection. Our findings revealed that 17.7% of cases were clinically documented episodes, aligning with reported ranges of 20 to 40% in other studies.[10] This variance may be attributed to the extent of evaluation and stringent antimicrobial prophylaxis protocols. Remarkably, 41% of our cases fell under the category of AFI-NOS. This proportion is similar to that observed by Hakim et al, who reported almost half of febrile neutropenia episodes as AFI-NOS, even with the use of comprehensive diagnostic tools.[10] Intriguingly, all AFI-NOS episodes in our study exhibited an indolent clinical course, a trend consistent with findings in the broader literature.[2,10] Furthermore, AFI-NOS cases were associated with a significantly shorter duration of neutropenia compared to both microbiologically and clinically documented infections.

Bacteremia (56.7%) was the most common cause of MDI. Blood culture positivity rate in our study was 23.3%, while other studies showed a rate of *bacteremia* ranging from 10 to 30%.[8,10–12]

The practice of obtaining dual cultures confers several advantages, including the identification of true bacteremia, the exclusion of potential contaminants, and the prevention of unwarranted central line removal. Notably, a study revealed that 97% of health care professionals would opt for peripheral blood cultures if there was a risk of missing true bacteremia exceeding 10%.[13] In the study conducted by Handrup et al, 17% confirmed bloodstream infections were diagnosed through cultures from peripheral veins, despite simultaneously obtaining blood cultures from central venous lines yielding negative results.[6] Our study aligns with these findings, demonstrating that 14.3% of confirmed bacteremia episodes were identified based on peripheral blood culture positivity. These consistent outcomes underscore the critical importance of acquiring paired cultures in clinical practice, reinforcing the value of this approach in accurately diagnosing bloodstream infections while avoiding unnecessary interventions such as central line removal.

The presence of an indwelling central venous access poses an increased risk of infections. The CRBSI rate was 13.33%, with CONS being the predominant bacterial pathogen

isolated, followed by gram-negative organisms, *S. aureus* and *Candida* spp. Our finding was consistent with the studies done by Demirel et al.[14]

IFD is an important contributor to morbidity and mortality in pediatric febrile neutropenia episodes. IFD was considered in individuals experiencing prolonged fever beyond 4 to 5 days, exhibiting poor response to antibiotics, and concurrent severe neutropenia. In our study, fungal infection was suspected in 14 (16.6%) episodes; however, only 3 (3.3%)) were proven.

Viral infections were identified in 16% of microbiologically documented cases, with a consideration of viral etiology grounded in the local epidemiological patterns of viral epidemics. Notably, the range of 5 to 25% in viral serology positivity documented in other studies underscores the potential influence of diagnostic test availability in different settings.[10,15] The variability observed across studies may be attributed to the diverse capacities for diagnostic testing in distinct health care setups.

During the influenza epidemic, of the five suspected cases tested by PCR, one was found to be positive. Children were started on empirical oseltamivir with barrier precautions and contact prophylaxis.

As our state is an endemic area for dengue virus, high suspicion for dengue fever was maintained. Dengue fever was suspected in children who presented with fever and nonspecific complaints of vomiting, abdomen pain, and myalgia. We had two confirmed cases of dengue.

The respiratory tract continues to be the most common site of infection. Chest X-ray imaging was selectively performed in children exhibiting symptoms of respiratory tract involvement. A study demonstrated low yield of routine chest X-rays, conducted at the time of admission for febrile children with chemotherapy-induced neutropenia who lacked respiratory symptoms.[16] Our investigation identified significant findings in 14.4% of cases. Predominantly, these findings included peribronchial infiltrates, followed by acute respiratory distress syndrome (ARDS), lobar consolidation, bronchiectasis, and hyperinflation. Remarkably, 9 (75%) of cases with notable chest X-ray findings were associated with MDIs, whereas 3 (25%) cases were clinically documented infections. This underscores the utility of targeted chest X-ray imaging in identifying specific respiratory complications during episodes of febrile neutropenia.

The bacterial spectrum is undergoing a reported shift from gram-negative organisms to gram-positive organisms, attributed to factors such as aggressive empirical gram-negative antibacterial therapy and the use of implantable devices.[10,11] In our study, gram-positive organisms were more prevalent (61.9%) than gram-negative organisms (38.1%). Notably, CONS emerged as the predominant isolate among gram-positive organisms (30.7%), followed by *Streptococcus* spp. Although CONS is often considered a skin contaminant, dismissing its growth in children with neutropenia would be precarious. Consequently, we opted for treatment wherever deemed prudent. Consistent with our findings, studies by Hakim et al,[10] Kamana et al,[11] and Soumya and Ajit Kumar[8] also highlighted a shifting trend toward gram-positive sepsis.

Examining our gram-positive profile, we found that 71% were resistant to penicillin, 50% were resistant to cloxacillin, and 28% were resistant to clindamycin. However, all isolates demonstrated sensitivity to vancomycin, teicoplanin, linezolid, and levofloxacin. Turning attention to gram-negative organisms, 60% exhibited resistance to third-generation cephalosporins, 50% to fluoroquinolones, and 33% to piperacillin-tazobactam and meropenem. The resistance pattern was notably more extensive and concerning among gram-negative pathogens, as depicted in graphs 3 and 4. These findings underscore the urgent need for robust antibiotic stewardship to mitigate the emergence of MDR pathogens.

The goal of initial empirical antibiotic therapy is to prevent serious morbidity and mortality, till the culture sensitivity is available. Although gram-positive organisms were common, gram-negative bacteremia were associated with greater morbidity (16.7 vs. 61.5%) and had a higher probability of being resistant. In our study, piperacillin-tazobactam and amikacin were used as empirical antibiotics, based on the local epidemiological trend. A systematic review by Lehrnbecher et al of randomized trials on comparison between monotherapy and aminoglycoside-containing combination regimens for febrile neutropenia found that the effects were similar.[17] We initiated empirical antifungal therapy beyond day 4 of febrile neutropenia and did not notice any higher incidence of IFD than other contemporary studies.[18]

In children with acute AFI-NOS, antibiotics were given until the preliminary cultures were negative and had been afebrile for 24 hours. In children with clinically documented bacterial infection, antibiotics were continued until the bacteria were completely eradicated. Bone marrow recovery is of paramount importance in eradication of infection. Several studies have shown that the risk of recurrent fever is low in patients with definitive marrow recovery.[17,19]

Prophylactic use of G-CSF has been shown to reduce the incidence of neutropenic fever in a variety of studies and meta-analysis reports.[20] In our practice, we do not consider prophylactic G-CSF in *hematological* malignancies.

In our study, we found poorer outcomes (morbidity and mortality) among gram-negative septicemia, likely because of increasing rates of antibiotic resistance. Mortality was 3.33% in our study, whereas other pediatric febrile neutropenia studies report mortality rates ranging from 0.5 to 6.6%.[10,21]

Conclusion

Febrile neutropenia, predominantly encountered in hematological malignancies and during intensive chemotherapy phases, poses diagnostic challenges often due to a lack of inflammatory response despite harboring potentially serious pathogens. Employing paired cultures aids in identifying true bacteremia. The chemo-port carries prime importance in the management of high-risk malignancies, and protocol-based management of CRBSI is necessary as it can limit the number of chemo-port removals.

The respiratory tract remains the predominant focus, and chest X-ray imaging proves highly beneficial when clinical features suggest respiratory tract infection. Despite the rise in gram-positive organisms, gram-negative organisms still account for significant morbidity. Therefore, early initiation of empirical antibiotics with antipseudomonal and extended-spectrum beta-lactamases (ESBL) coverage, along with optimal gram-positive coverage, is crucial. Aggressive evaluation and treatment of suspected fungal infections in children are essential. Prolonged neutropenia lasting beyond 96 hours, with persistent fever, necessitates empirical antifungal therapy in high-risk individuals. Moreover, if access to IFD workup is readily available, preemptive antifungal therapy can be considered in low-risk individuals. Additionally, viral infection workup in relevant clinical settings significantly reduces unnecessary antibiotic use. Notably, infection-related mortality was as low as 3.3% in our study, underscoring the efficacy of an organized and protocol-based approach in managing this fatal complication.

Learning Points

- Children undergoing cancer chemotherapy face heightened susceptibility to severe infections, which necessitate prompt treatment to prevent rapid deterioration.
- Crucial aspects of managing febrile neutropenia include identifying the focus of infection and determining the causative pathogens.
- Forming a multidisciplinary team comprising oncologists, infectious disease specialists, and microbiologists is crucial for crafting institutional protocols to manage febrile neutropenia, customized to local antibiogram data.
- Prompt and aggressive evaluation and treatment of febrile neutropenia are critical for optimal outcomes in pediatric cancer patients undergoing chemotherapy

Authors' Contribution

A.M. contributed to the concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. N.G.H. contributed to the definition of intellectual content, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. A.S. contributed to the concepts, design, definition of intellectual content, manuscript editing, and manuscript review, and is also a guarantor. R.T. contributed to the concepts, design, and manuscript review, and is also a guarantor.

Patient Consent

Patient consent was obtained for this study.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We would like to acknowledge all the parents for providing the opportunity to study on the pattern of febrile illness. We are grateful to the members of our department of laboratory sciences for their immense contribution in patient care.

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Role of Cell-Free DNA in Relapsed Head and Neck Cancer

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Ind J Med Paediatr Oncol 2025;46:87–92.

Abstract

Introduction Owing to the aggressive biology of head and neck squamous cell carcinoma (HNSCC), new biomarkers that can facilitate the diagnosis and tracking of tumour growth are the need of the hour. Liquid biopsy has emerged as an easier tool than tissue biopsy to monitor the emergence of treatment resistance or the recurrence of disease at the molecular level.

Objectives To assess the role of cell-free DNA (cfDNA) as a biomarker for relapsed HNSCC.

Materials and Methods This study is a Phase 2 interventional study (NCT: CTRI/2020/02/023378) that assessed the response rates of a new triplet drug regimen in refractory or relapsed HNSCC. Thirty-five patients underwent blood sampling before the commencement of therapy and at 3 months of treatment. Isolation of cfDNA was done using magnetic beads (molecular weight near 170 kb) for quantification.

Results Twenty-eight patients had comparable data at baseline and after 3 months oftreatment. The mean cfDNA reading at baseline was 8.9 ng/μL (range: 2.6 -7.3 ng/μL) of blood. The cfDNA concordance with clinical and radiological outcomes was 54.2%. The patients who responded to therapy were compared over time with patients who did not respond. Repeated measures testing found a significant difference (p 1?4 0.0035) in changes to the cfDNA levels of these two groups.

Conclusion This study posits the potential value of liquid biopsy in the treatment ofrecurrent HNSCC. Our findings prove the clinical relevance as well as limitations ofcfDNA, which warrant extrapolation in an upfront setting too.

Keywords
- molecular biomarker
- recurrence risk
- resistance
- cell-free DNA
- head and neck tumors
- liquid biopsy
- mutations

Introduction

Despite the progress brought about by the latest advances, head and neck squamous cell carcinoma (HNSCC) has a high relapse rate. The resultant demand for ongoing treatment has a huge impact on the health system.[1,2] The assessment of head and neck cancer is done using clinical and radiological methods. The identification of new biomarkers that can aid the evaluation of HNSCC is an unmet need, particularly given that relapses are common and aggressive.

article published online
December 13, 2024

DOI https://doi.org/10.1055/s-0044-1792008.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Liquid biopsy has expanded the range of biomarkers that can be used to analyze disease status.[3,4] Circulating tumor DNA (ctDNA) (derived from cancer cells) has been identified as a subset of the total circulating cell-free DNA (cfDNA) in the bloodstream. While total cfDNA is formed under several conditions, ranging from infection to trauma, ctDNA is believed to be shed by tumor cells that are undergoing apoptosis or necrosis.[5,6] Recently, cfDNA and ctDNA have been gaining popularity as novel blood biomarkers because their quantification, kinetic analysis, and molecular profiling have been found to have predictive and prognostic importance.[7]

The advent of liquid biopsy, a multimodal diagnostic tool, has drastically altered existing perspectives on the management of HNSCC.[8] Nevertheless, prospective studies identifying the role of liquid biopsy in HNSCC are limited. Saliva, tumor tissue, and plasma have been utilized for this purpose.[9] Blood (plasma) is a preferable option for quantifying cfDNA because it contains a higher concentration of ctDNA, is more stable, and is less prone to contamination, unlike saliva. It is simpler to collect and provides a more accurate snapshot of ctDNA than tumor tissue, which involves more invasive collection procedures. In this study, we envisaged utilizing cfDNA as a biomarker using plasma to identify responders or nonresponders and determined the existence of a correlation with survival outcomes in recurrent/metastatic HNSCC.

Materials and Methods

Study Design

Our study was a Phase II interventional study (NCT: CTRI/2020/02/023378) that evaluated the response rates of a new triplet regimen in relapsed/refractory head and neck cancer. This single-arm study was conducted at our head and neck cancer clinic at the All India Institute of Medical Sciences in New Delhi, after institutional ethical committee approval and Clinical Trials Registry—India registration were granted. Participating patients underwent palliative chemotherapy (every 28 days) as the intervention—EMF regimen: tablet erlotinib 150 mg OD, and injection methotrexate 40 mg/m^2 and injection 5-fluorouracil 500 mg/m^2 given intravenously on days 1 and 8 of every 28-day cycle. The primary objective was to assess the response rates of the triplet regimen (EMF). The sample size was calculated as per Simon's two-step design for a Phase II study. Assessments were done at 3-month intervals, using contrast-enhanced computed tomography via Response Evaluation Criteria in Solid Tumors 1.1 criteria. The primary outcome was to assess the objective response rate with the EMF regimen and has been described earlier in the study by Baa et al.[10] The secondary outcomes of the study were to assess the utility of cfDNA and circulating tumor cells (CTCs) as biomarkers, and correlation with survival outcomes in HNSCC was evaluated as an exploratory analysis. Our data on CTCs in relapsed/metastatic HNSCC has already been reported.[11] Herein, we elaborate the role of cfDNA as a predictive biomarker as a secondary focus of our research.

Inclusion criteria were as follows:

1. Histopathological diagnosis of squamous cell carcinoma of head and neck region.
2. Age >18 and ≤ 70 years.
3. Eastern Cooperative Oncology Group performance status 0 to 2.
4. Recurrence of disease within 6 months after definitive or on palliative therapy.
5. Previous exposure to platinum agents either as chemotherapy or part of concurrent chemoradiotherapy.
6. Recurrence after treatment with PDL1 inhibitors.
7. Adequate organ function including absolute neutrophil count $>1{,}000/mm^3$, platelets $>100{,}000/mm^3$; normal liver function test (serum bilirubin <2 mg/dL, aspartate transaminase <3X upper limit of normal [ULN], alanine transaminase <3X ULN, alkaline phosphatase <3X ULN); and renal function tests (glomerular filtration rate >50 mL/min).
8. Financial constraints for cetuximab, nivolumab, and pembrolizumab.
9. Measurable disease.

Exclusion criteria were as follows:

1. Uncontrolled severe comorbidities.
2. HIV positivity, HBsAg, or HCV-related hepatitis.
3. Nasopharyngeal carcinoma/sinonasal carcinoma.

Quantification of Cell-Free DNA

Venous blood samples (2–3 mL volume) were drawn under aseptic precautions in a BD vacutainer (K2 EDTA 10.8 mg) for the extraction of plasma. Serial plasma was collected before the initiation of therapy and again at 3 months. The sample collected was allowed to stand for 30 minutes, followed by centrifugation at 2,000 rpm for 10 minutes. Next, 1 mL of plasma was extracted and stored at $-80°C$. We used Maxwell kit and Promega Maxwell station to quantify cfDNA levels. The isolation of cfDNA was done using magnetic beads. The prefilled cartridges and absence of preprocessing steps help purify high-quality cfDNA in a simple three-step protocol. The use of a magnetic particle mover, as opposed to a liquid handler, offers advantages over other automated systems. The risk of cross-contamination was minimal because no liquid handling or splashing occurred during sample processing. The levels of cfDNA were directly measured on a nanodrop reader. The representative gel after the isolation of cfDNA using a magnetic bead yielded a molecular weight near 170 kb (►**Fig. 1**).

Statistical Analysis

The software package IBM SPSS v.26 was used for data analysis. Details of the baseline characteristics were reported earlier.[10,11] The survival outcomes were assessed by Kaplan–Meier curves, and a repeated measures test was used to evaluate the difference in responses over time. The tools used in this study are similar to the tools we incorporated when

we reported our overall response rates and the role of CTCs as biomarkers in relapsed/metastatic HNSCC.[10,11]

Ethical Approval

The study was conducted after approval was granted by the Institute Ethics Committee for Postgraduate Research, All India Institute of Medical Sciences, New Delhi (ref. no. IECPG-IECPG-755/30.01.2020,OT-18/23.09.2020). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Results

Analysis of cfDNA

The mean reading at baseline was 8.9 ± 3.9 ng/µL for our entire cohort of 35 patients. Comparable data at two time points (0 and 3 months) were available only for 29 patients. The concordance and discordance rates with responses were 54.2 and 25.7, respectively, while these rates were not evaluable for 17.1% of the patients (►**Table 1**). The details of the responses (partial response/stable disease/progressive disease) achieved for each patient are presented in ►**Fig. 2**. A statistically significant difference ($p = 0.035$) in cfDNA levels with time was seen in responders and nonresponders when repeated measures time test was done. This finding corresponds with what our data described for CTCs as a marker.[11] The mean cfDNA readings declined for responders after 3 months of therapy (9.8 ± 4.5 ng/µL to 6.6 ± 3.1 ng/µL), while the nonresponders displayed an increase in their levels (7.4 ± 1.69 ng/µL to 8.5 ± 2.1 ng/µL) (►**Fig. 3**, ►**Table 2**).

Table 1 The concordance/discordance in cfDNA levels in response to palliative chemotherapy

Response: partial response/stable disease No response: progressive disease	
Parameter	***N* (%)**
Concordance	19 (54.2)
Discordance	9 (25.7)
Not evaluable	6 (17.1)

Abbreviation: cfDNA, cell-free DNA.

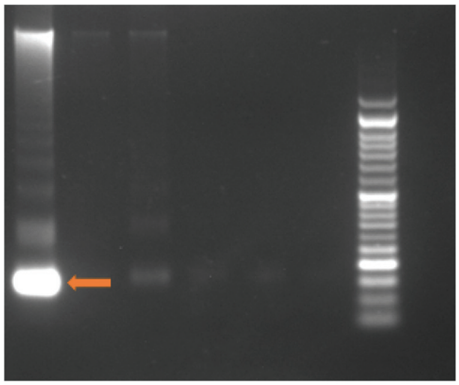

Fig. 1 Representation of gel electrophoresis of cfDNA. Arrow indicating cfDNA with a molecular weight of 170 kb. cfDNA, cell-free DNA.

Survival analysis progression-free survival (PFS) and overall survival (OS) with baseline cfDNA levels (> 9 and < 9) were estimated (►**Figs. 4** and **5**; ►**Table 2**). The median PFS was 6 months (95% confidence interval [CI]: 5.2–6.7) and the median OS was 7 months (95% CI: 5.6–8.9) in the cohort with

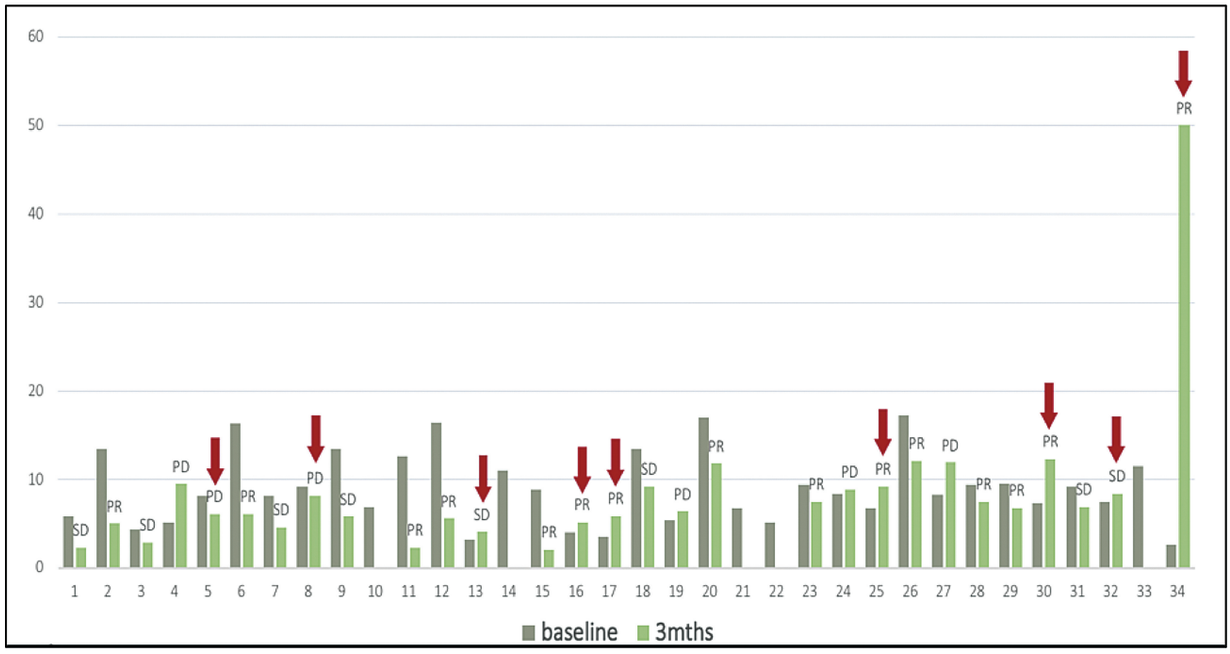

Fig. 2 Bar graph showing cfDNA levels at 0 (gray) and 3 (green) months. The response for each patient is labeled (PR/SD/PD); red arrows indicate discordance. cfDNA, cell-free DNA; PD, progressive disease; PR, partial response; SD, stable disease.

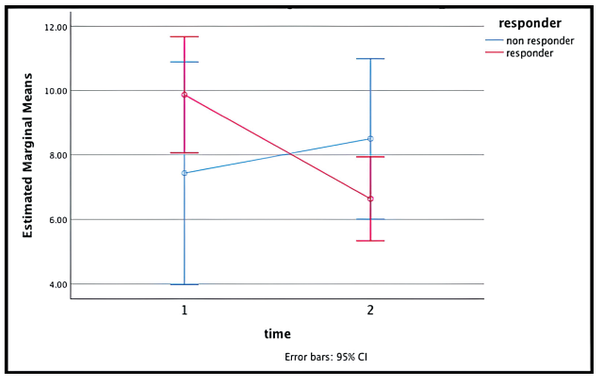

Fig. 3 Repeated measures test showing difference in cfDNA levels with time in the patients who had a response (red) versus no response (blue). The difference was statistically significant ($p = 0.035$). cfDNA, cell-free DNA; CI, confidence interval.

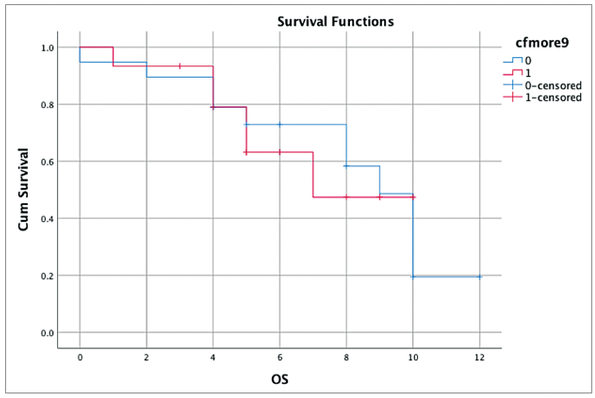

Fig. 5 Survival outcome—overall survival (OS) with baseline median cell-free DNA.

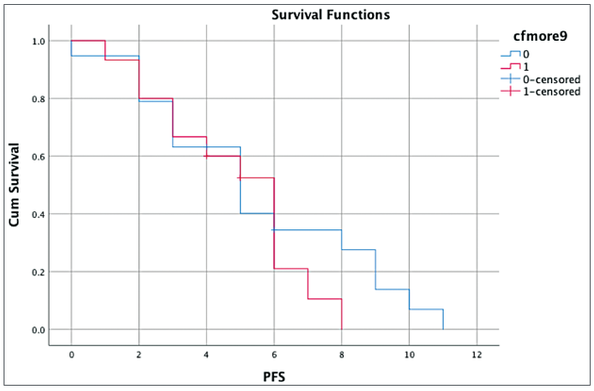

Fig. 4 Survival outcome—progression-free survival (PFS) with baseline median cell-free DNA.

baseline cfDNA >9, while it was 5 months (95% CI: 2.7–7) and 9 months (95% CI: 7.6–10.3), respectively, in the cohort with baseline cfDNA levels <9 (►**Table 2**).

The patients presented with a high volume of disease, characterized by swelling and ulceration (79%), followed by significant lymph node enlargement (17%). The differences in baseline cfDNA levels based on the site of origin were compared. The mean reading was higher for the tumors arising from the oral cavity (buccal mucosa predominantly) amounting to 9.39 ± 4.87 ng/μL (►**Fig. 6**, ►**Table 3**). Also, the exposure to radiotherapy as part of the concurrent chemoradiotherapy protocol was associated with lower cfDNA levels (7.59 ± 2.84 ng/μL) when compared with those who did not (11.61 ± 5.1 ng/μL) (►**Table 4**).

Table 3 Differences in baseline cfDNA levels based on the site

Location	Mean ± SD (ng/μL)
Oral cavity	9.39 ± 4.87
Oropharynx	7.75 ± 1.89
Others (hypopharynx/larynx)	8.53 ± 3.7

Abbreviations: cfDNA, cell-free DNA; SD, standard deviation.

Discussion

Precision medicine has revolutionized the management of oncology. Liquid biopsy based on cfDNA analysis is one promising tool that is being explored in the treatment of many solid tumors.[3] Surani and Poterlowicz described the release of cfDNA in the system. Contributing factors are physiological mechanisms, such as apoptosis, necrosis, active secretion, and other events induced by microenvironmental stress and treatment pressure.[12] cfDNA is a combination of noncancer cell DNA from normal cells and ctDNA from cancer cells. The median cfDNA levels are higher in patients with malignancies than in healthy individuals.[3]

The mean cfDNA quantified in our cohort using the Maxwell kit (with magnetic beads) at baseline was 8.9 ± 3.9 ng/μL. Lin et al (2018) studied cfDNA levels using quantitative spectrometry in 121 patients with HNSCC. The average size reported in their study was ~150 to 200 bp.[13] However, our study demonstrated higher cfDNA levels, probably because of the heavy burden of disease, extensive locoregional involvement, and participating patients being in a relapsed metastatic setting. Verma et al also reported high cfDNA levels in HNSCC patients undergoing

Table 2 PFS and OS correlation with baseline cfDNA

cfDNA at baseline	Median PFS, mo (range)		Median OS, mo (range)	
>9	6 (5.2–6.7)	$p = 0.61$	7 (5.6–8.9)	$p = 0.98$
<9	5 (2.9–7)		9 (7.6–10.3)	

Abbreviations: cfDNA, cell-free DNA; OS, overall survival; PFS, progression-free survival.

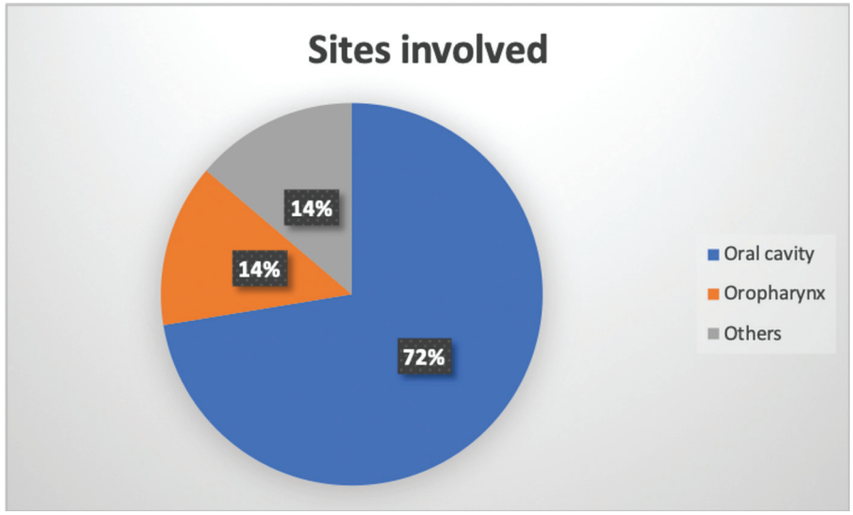

Fig. 6 Figure showing common sites involved.

Table 4 Differences in baseline cfDNA levels based on exposure to radiation

Radiation (CTRT)	Mean ± SD (ng/μL)
Yes	7.59 ± 2.84
No	11.61 ± 5.1

Abbreviations: cfDNA, cell-free DNA; CTRT, combined chemoradiotherapy; SD, standard deviation.

chemoradiation, which correlated with a higher nodal burden.[14] This study compared the cfDNA level of patients with controls, which was lacking in our study. Verma et al used a β-globin assay to quantify the levels, while our estimation was done directly via the nanodrop technique. Another study prospectively analyzed plasma cfDNA as an early biomarker in patients undergoing radiotherapy, which showed that posttreatment higher levels were associated with early relapses.[15] However, we attempted the estimation prospectively, in a palliative setting where patients had platinum-resistant/refractory disease and the differences in cfDNA levels based on exposure to radiotherapy were revealed. The patients unexposed to radiation had a higher baseline cfDNA level compared with those receiving radiation as a part of definitive or palliative chemoradiotherapy.

Another study, by Mazurek et al, used TaqMan-based TERT amplification to quantify the cfDNA levels of 200 HNSCC patients.[16] The anatomical site (oropharyngeal vs. others) and lymph nodal burden (N2–N3 vs. N0–N1) were significantly associated with higher cfDNA levels ($p = 0.011$).[16] Our study supports this finding, as the mean baseline values are on the higher side. Also, the levels were more elevated in patients with tumors arising in the oral cavity, especially buccal mucosa. This concurs with the results seen in the study by Brandt et al.[9]

The concordance and discordance rates with clinical and imaging-based responses were 55.8 and 26.4%, respectively, while they could not be assessed for 14.7% of the patients. Using the repeated measures test, a statistically significant difference ($p = 0.035$) in cfDNA levels was found with time between responders (decline in mean baseline cfDNA levels from 9.8 ± 4.5 to 6.6 ± 3.1 at 3 months) and nonresponders (rise in mean baseline cfDNA levels from 7.4 ± 1.69 to 8.5 ± 2.1 at 3 months) (►**Fig. 3**, ►**Table 2**).

Limitations of the Study

In this study, we have attempted to see the differences in the cfDNA levels of responders and nonresponders. This focus was lacking in previous studies. As has been reported, higher cfDNA levels are associated with a poor prognosis.[13,14,16] However, we did not observe any significant differences in the PFS and the OS based on a comparison of baseline cfDNA levels (> 9 or < 9). The reason may be that the crude method of cfDNA estimation leads to discordant results. The small sample size might also be a factor. Utilizing the housekeeping genes for quantification would add more robust data. Another point that must be considered is that raised cfDNA levels are also observed in infective and inflammatory conditions.[13,14,16–18] Therefore, the presence of comorbidities must be taken into account when interpreting the quantification of total cfDNA. Hence, the positive predictive value of cfDNA is limited by the confounding factors of poor oral hygiene, and infection that were commonly observed in our HNSCC patients.

Furthermore, as this was a single-arm study with fewer patients and no controls, there were limited data to analyze and compare. It was an exploratory analysis, as a part of our translational effort in HNSCC, and was not powered enough to establish definite conclusions and correlations. Currently, liquid biopsy is a difficult technique to access for the majority of our population. The financial constraints also pose a challenge to adequately explore this new tool.

Conclusion

This study explores cfDNA as a predictive biomarker in the treatment of HNSCC. The heavy burden on health systems of

recurrent/metastatic HNSCC, with its aggressive biology and poor response rates, makes its management challenging. The identification of new biomarkers is therefore an urgent need. Our findings could be extrapolated to upfront settings to predict treatment response and detect early relapses. The incorporation of biomarkers such as cfDNA could provide invaluable support to the existing tools used in the treatment of such complicated diseases with high recurrence rates.

Patient Consent

Patient consent was obtained for this study.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

We thank our patients and family for their cooperation.

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Incendiary Appearance of a Scalp Lesion: Whether Benign or Malignant?

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Ind J Med Paediatr Oncol 2025;46:93–95.

Case Summary

A 46-year-old woman presented to the surgical outpatient department with a 10-year history of scalp swelling in the occipital region. The swelling was initially small in size, which gradually increased to attain the size of a pebble (►**Fig. 1**). There was no history of trauma preceding the onset of swelling. The patient did not complain of any pain, itching, or discoloration. On examination, the skin overlying the swelling was normal. The swelling was freely mobile in all directions and was not adherent to overlying skin or underlying structures. The consistency was soft to firm on palpation. The patient underwent surgical excision, and the specimen was sent for histopathological examination.

Differential Diagnosis

The differential diagnoses considered on clinical examination in this case were lipoma, epidermoid cyst, and sebaceous cyst.

Histopathological Workup

Gross Examination

A partially skin-covered globular tissue mass measuring $2.0 \times 1.4 \times 0.8$ cm was observed. It had a well-demarcated solid cystic swelling with a glossy white cyst wall (►**Fig. 2**). The cut surface showed a firm whitish ovoid area measuring $1 \times 0.6 \times 0.6$ cm with other cystic area filled with yellowish material (►**Fig. 3**).

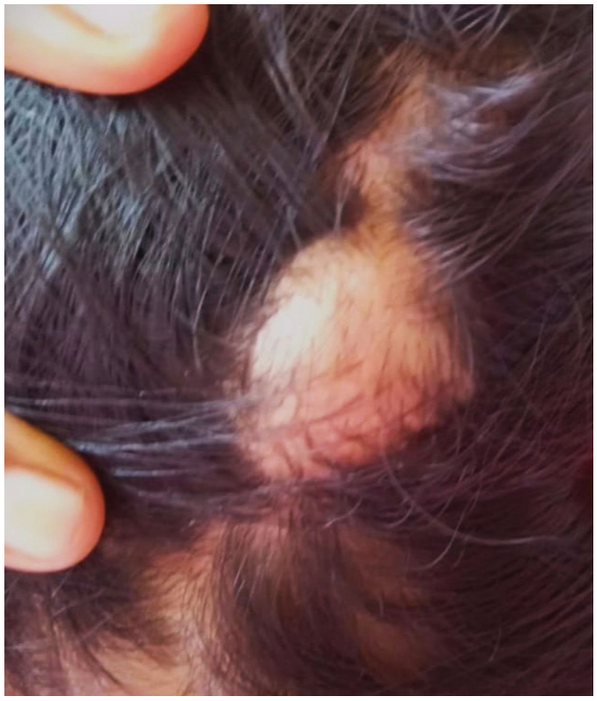

Fig. 1 Swelling in occipital region of the scalp. The overlying skin appears normal.

Microscopy

The cyst wall was lined by a keratinized stratified squamous epithelium with the absence of a granular cell layer. Variable sized lobules of squamous epithelium were noted

article published online December 13, 2024

DOI https://doi.org/10.1055/s-0044-1795093.
ISSN 0971-5851.

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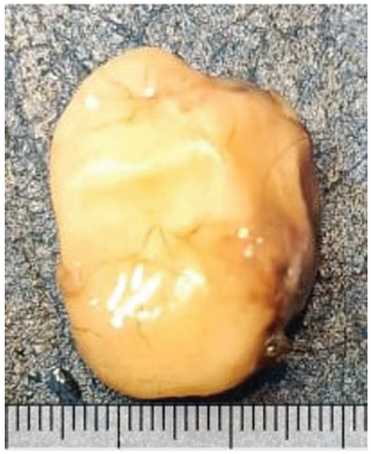

Fig. 2 Excision biopsy of the scalp lesion. The outer surface is glossy white in appearance.

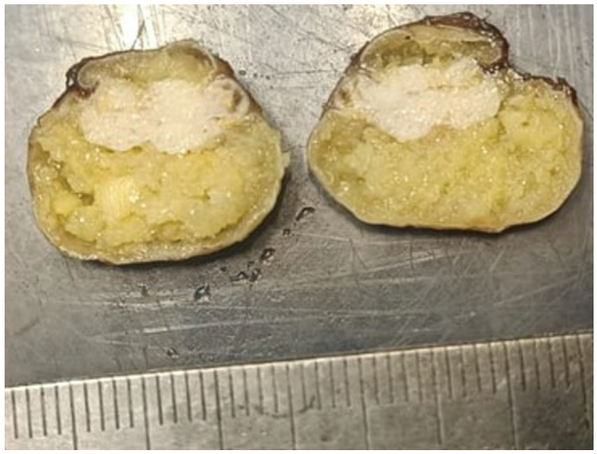

Fig. 3 The cut surface of the solid cystic lesion, which showed a firm whitish ovoid solid area with other cystic area filled with yellowish material.

undergoing abrupt change into eosinophilic amorphous keratin. The proliferating epithelium showed pushing borders. The cyst cavity contained abundant keratin, cholesterol clefts, and areas of calcification. No granuloma or giant cells were present. No dysplasia existed (►**Figs. 4**–**7**).

Diagnosis and Discussion

The low-power histomorphology of the lesion may mimic the appearance of a squamous cell carcinoma. However, the important differentiating points that need to be considered here are pilar-type keratinization, absence of a granular layer, presence of a well-defined capsule, and the presence of the proliferating part only within the capsule, which support the diagnosis of a proliferating pilar tumor.

This tumor was first described by E.W. Jones who referred to it as a proliferating epidermoid cyst, which

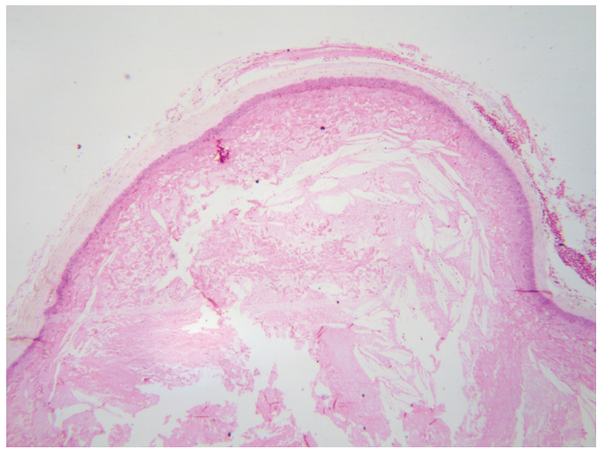

Fig. 4 Cystic cavity lined by keratinized stratified squamous epithelium with the absence of the granular layer. Cholesterol clefts are also evident (hematoxylin and eosin, ×40).

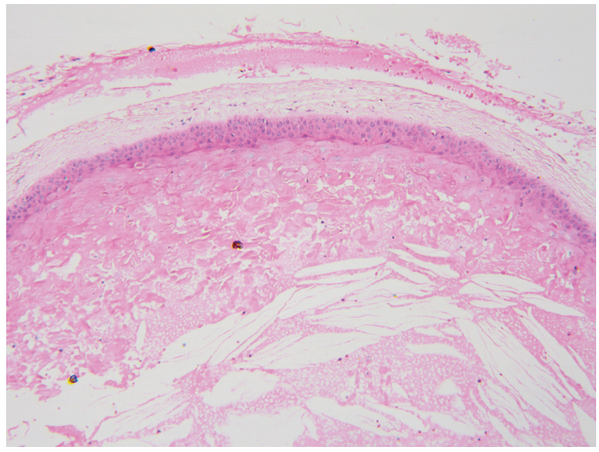

Fig. 5 Similar findings as in Fig. 4 but at a higher magnification. The keratin-filled cavity is better appreciable at this magnification (hematoxylin and eosin, ×100).

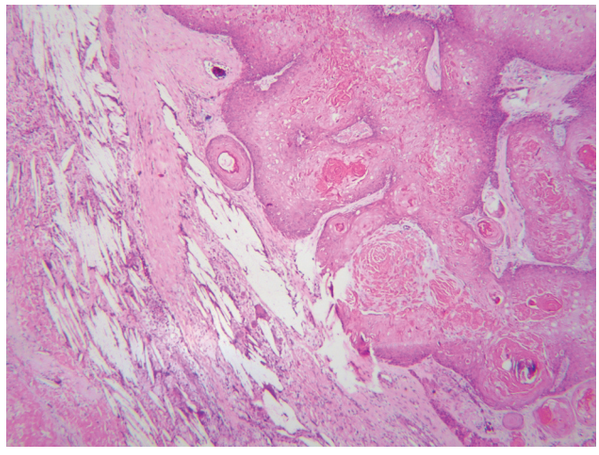

Fig. 6 Variable sized lobules of squamous epithelium undergoing abrupt change into eosinophilic amorphous keratin. The proliferating epithelium shows pushing borders. The lesion is considered a mimic of squamous cell carcinoma (hematoxylin and eosin, ×40).

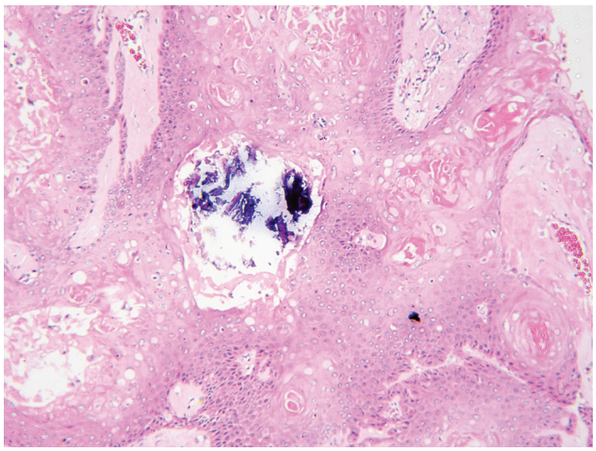

Fig. 7 Areas of calcification, which commonly occur in proliferating pilar tumors.

has also been called a proliferating pilar tumor.[1] Other terms that are used for the condition include proliferating trichilemmal cyst, proliferating trichilemmal tumor, and pilar tumor of the scalp.[2] Although this has been considered a benign mimic of squamous cell carcinoma, there are few reports describing the malignant behavior of these tumors.[3,4] Most cases are noted in women in the 43- to 66-year age range, with the most common location being the scalp.[5] The incendiary appearance of this lesion may create a diagnostic dilemma, but a thorough microscopic examination would lead to a definite diagnosis.

Patient Consent

The authors certify that they have obtained all appropriate patient concent forms. in the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Funding

None.

Conflict of Interest

None declared.

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Developing a Collaborative Research Environment in Health Care: Challenges and Opportunities

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Ind J Med Paediatr Oncol 2025;46:96–98.

Introduction

In health care research, the importance of interdisciplinary collaboration between psychologists, technologists, and health care professionals cannot be overstated.[1] Interdisciplinary research holds transformative potential to facilitate a holistic understanding of the factors that enable the implementation of targeted interventions to mitigate risks and enhance patient outcomes.[2–4] It is a vital conduit for enriching research outcomes, by integrating psychological insights as a leverage to drive technological developments.[5] To improve our understanding of the clinical relevance of the sample, it was necessary for us to comprehend the nuances of both disciplines.

Navigating the landscape of hospital-based field research can pose an array of challenges ranging from issues with data collection procedures to cooperation from health care professionals or suspending the underlying sense of suspicion related to research.[6–8] These challenges can arise due to various factors, such as busy schedules, competing priorities, and institutional bureaucracy.[9] Obtaining necessary approvals and permissions can be an exhausting process given the multiple layers of review and coordination with hospital administrators and ethics committees.[10] More importantly, engaging with health care professionals can be challenging due to skepticism and perceived intrusion into clinical activities.[11] Demanding schedules and diverse commitments affect the availability and participation of health care professionals in research activities.[12] It is crucial to recognize and acknowledge that this can impede the data collection process.

Drawing from personal experiences as field researchers, these obstacles underscore the necessity for garnering support for research initiatives.[9] In such endeavors, the acquisition of certain skills over time becomes imperative, namely effective communication, adaptability, and technical proficiency.[13] For instance, when engaging with doctors, their primary focus often revolved around understanding the technical aspects and mechanisms behind the new device or intervention under investigation. Conversely, when communicating with nurses, they were particularly interested in how the new device or intervention could improve efficiency, and enhance patient outcomes in day-to-day routines. Additionally, they also highlighted that patient-related factors, such as comorbidities, demographics, and clinical history, were considered in the research design and implementation.[2]

For successful fieldwork, fostering rapport is a linchpin, especially when collaborating with nurses who play a pivotal role in the health care ecosystem.[14] Despite facing initial skepticism, nurses became staunch allies, providing invaluable support and guidance throughout the research process.[15] They played a pivotal role in making the whole process of interviewing patients less intimidating for the patients and those collecting data from them, thereby enabling a smoother research process.[16] Their intimate familiarity with the daily realities of clinical practice, nuanced understanding of patient needs and experiences, and hands-on engagement with health care technologies render them invaluable collaborators in the research process.[17]

Operating within multidisciplinary teams demands adeptness in approaching several different individuals for the successful accomplishment of research tasks.[18] Tailoring communication strategies to effectively engage with diverse stakeholders and address their specific interests and concerns also becomes important.[1] It becomes crucial to adapt language to suit the needs of the context, such as using technical terms that focus on usability for tech teams and emphasizing practical implications for clinicians.[19] As we moved further ahead in research by introducing the developed instrument into the field, there was a constant need for

article published online
December 11, 2024

DOI https://doi.org/10.1055/s-0044-1795112.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

change in language and narrative with each stratum of the population, for example, there was a considerable difference in what constituted an idea of convenience, reliability, dependability, and other related metrics to the personnel developing the instrument from that of the health care professionals who were to utilize this architecture in the field practically.[20] Therefore, it has become of great importance to map the changes of the instrument moving from an experimental laboratory to a clinical one.[13] Conversely, challenges with patients and their caregivers can be based on contextual comprehension, where we had to explain the need and uses of the instrument.[21] Given the diverse patient sample across critical care, pediatric, and geriatric populations, technological integration, advocacy, and understanding confidentiality were a few challenging areas.[22] It was important to have patience while empathizing with their circumstances and requirements. A large number of people expressed their emotions existentially, downplaying their challenges in light of the more severe illness they were facing. As psychologists, we bridge this gap, conveying the needs of both groups to optimize patient outcomes.[23]

In our personal experience, data collection in a clinical environment differs significantly from other settings due to the constant prioritization of emergencies and critical situations.[24] Quoting back on the issue of scheduling interviews with health care professionals, it is only appropriate that patient well-being is given precedence over other activities in a hospital setting.[21] On the other hand, this also implies that we as a research team are provided with minimal time and resources to investigate the problem under study. Working in a field also entails that one repeats their observations over time—notice patterns, associate and un-associate cause and effects, and observe the behavior of the people involved in the study. Over time, we realize that there is often more to observe than one would imagine otherwise.[25] It is through these consistent and continuous observations that one can understand and analyze the variables under study, thereby necessitating the need for psychologists as the bridge between laboratory and field.[26]

Navigating through the complexities of hospital settings and collaborating with a diverse range of healthcare professionals also helped foster skills of adaptability and team work. It also instilled an understanding of professional conduct and cultivated a stronger sense of work ethic, which applies to every other workplace.[14] Additionally, this experience honed our skills in working with vulnerable populations and what precautions one must be mindful of taking with such groups.

This article highlights the critical importance incorporating psychological perspectives into biomedical research and its role in advancing the shared goal of enhancing patient care within both biomedical and psychological disciplines. It also focuses on the ground-level experiences of conducting research in hospital environments, which present unique challenges, such as difficulties in data collection and skepticism from health care professionals for which researchers must employ strong communication skills and adaptability to address the diverse needs of different stakeholders. By leveraging personal experiences, this study explores how psychologists function as a conduit between laboratory research and clinical practice. Their expertise in behavioral analysis and patient interaction is instrumental in making research findings more applicable and impactful in health care settings highlighting how the contributions are crucial for translating research into practical, patient-centered interventions. The overarching objective of this perspective study is to highlight the role of psychologists in bridging the divide between laboratory-based research and real-world clinical practice and shed light on the challenges inherent in conducting such interdisciplinary research.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
This research endeavor would not have been possible without the assistance of several people to whom we would like to express our sincere gratitude. We would like to thank all the health care professionals who helped us navigate and conduct research in the hospital landscape. We thank them for their patience and invaluable support in data collection activities. We would also like to thank the Department of Liberal Arts and the Department of Physics, Indian Institute of Technology, for having given us the opportunity to conduct field research and work on an interdisciplinary project. Finally, we thank all the participants who were a part of this research; their contribution is greatly appreciated.

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Skin Tumors in Pediatric Patients with Xeroderma Pigmentosum: A Case Series

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Ind J Med Paediatr Oncol 2025;46:99–103.

Abstract

Xeroderma pigmentosum (XP) is a rare autosomal recessive genetic disease. This disease predisposes patients to early-onset skin cancers, like squamous cell carcinoma and basal cell carcinoma. This was a 5-year experience. Here, we report nine pediatric cases of XP in which two patients had basal cell carcinoma and six patients had squamous cell carcinoma. We have also reported one case in which both skin malignancies were present. The subjects included seven boys and two girls, while seven subjects were from consanguineous marriages, and the average age was 9.4 years. All the patients had ulcerative budding tumor lesions on the face (eye, nose, chin, cheek, and forehead) and scalp. Squamous cell carcinoma is a common cutaneous malignancy related to XP in our study. Prevention is based on the early diagnosis of XP, skin photo-protection, screening and early treatment of lesions, and genetic counseling.

Keywords
- basal cell carcinoma
- squamous cell carcinoma
- xeroderma pigmentosum
- genetic disease
- skin cancers

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive genetic condition characterized by photosensitivity, ocular involvement, and neurological involvement.[1] The failure of DNA repair via the nucleotide excision repair pathway is the source of these symptoms, which are induced by cellular hypersensitivity to ultraviolet (UV) radiations.[2] Patients with XP have a 1,000-fold greater risk of cutaneous cancers such as basal cell carcinoma (BCC), squamous cell carcinoma, and malignant melanoma in sun-exposed areas.[3]

As previously stated, the prevalence of XP is quite high in Japan (1: 40 000),[4] although it is relatively low in the United States (1:250,000).[5] This genetic disorder has been documented across the border areas of Pakistan, Afghanistan, and Northern India.[6] According to a literature search, incidences of XP were documented in Larkana, Sibbi, Karachi, Lahore, and District Dir in Pakistan from 1993 to 2016.[7,8] To discover any common loss of heterozygosity in affected people, single-nucleotide polymorphism genotyping was done with Sanger sequencing on seven consanguineous families with XP in the Baluchistan region.[9] More XP cases have lately been reported in Pakistan's Baluchistan Province in 2021.[10]

Here, we present our 5-year experience with XP patients residing in this tropical region. We are reporting the clinical data on XP patients from Sindh province, which has hot humid weather with abundant sunlight for 8 of 12 months during the year. This study aims to evaluate 09 XP patients for the development of skin tumors, with their distinct clinical and histopathological features (►**Table 1**). The study was approved by the institutional ethical committee and conducted following the Declaration of Helsinki.

Methodology

Case Series

Case 1

A 5-year-old boy was a known case of XP, freckles, and pigmentary skin changes that occurred gradually at the age of approximately 2 months. His parents noticed an eruption

DOI https://doi.org/10.1055/s-0043-1768984.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

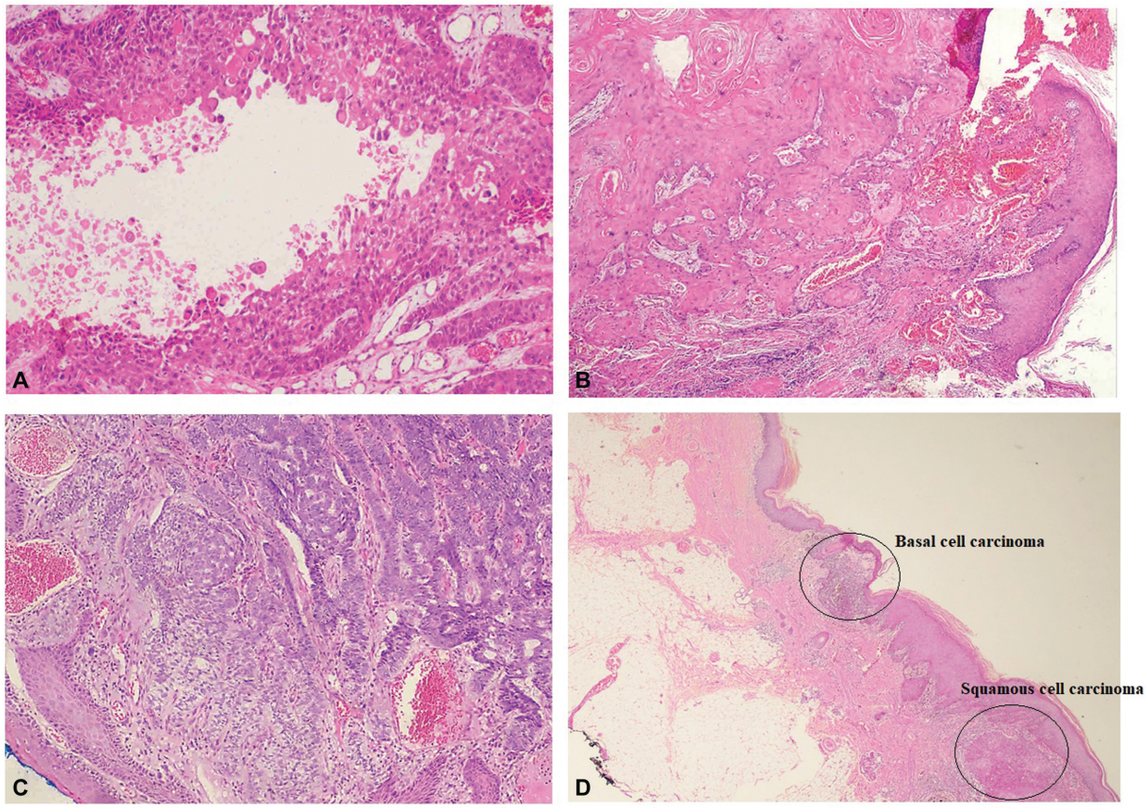

Fig. 1 (A) Acantholytic type squamous cell carcinoma. **(B)** Squamous cell carcinoma. **(C)** Basal cell carcinoma. **(D)** Squamous cell carcinoma and basal cell carcinoma.

on his forehead; they went to a local hospital where a biopsy showed squamous cell carcinoma. The boy underwent a scalp lesion excisional biopsy, the ulcerated lesion measured 2.5 cm. The histopathological findings indicated squamous cell carcinoma, tumor cell exhibited infiltration with marked dissociation, and features were consistent with squamous cell carcinoma, acantholytic type (►**Fig. 1A**).

Case 2

A 6-year-old boy, the first offspring of consanguineous marriage, and a resident of Naushahro Ferozebad, had skin pigmentation at the age of 6 months. His three relatives also have the same skin condition. They visited the local hospital where the patient was diagnosed with XP. He had multiple skin nodules for 2 years, a biopsy of the skin nodule was done in 2016 showing squamous cell carcinoma, and the boy had one lesion operated on 9 months back. They came to our hospital in 2017 with an exuberant tumor at the lower eyelid conjunctiva; excisional biopsy was done that showed squamous cell carcinoma (►**Fig. 1B**).

The patient was lost to follow-up, then again came in 2018 with three suspicious hypergranulating lesions on the scalp. The histopathological findings were consistent with moderately differentiated keratinizing squamous cell carcinoma. Wide-margin excision of the scalp was done; the lesion was completely excised. The immunohistochemical marker CK 5⁄6 was positive in neoplastic cells.

Case 3

A 14-year-old male child, the first offspring of a consanguineous marriage, and a resident of Karachi, was a known case of XP. He developed swelling in the right eye 1 year back that gradually increased in size and become ulcerated for 3 months. The right orbital mass biopsy was done that showed infiltrating neoplasm, and extensive surface ulceration was present with dense acute and chronic inflammation. The findings were consistent with moderately differentiated keratinizing squamous cell carcinoma. His surgery was done at another medical facility.

Case 4

An 11-year-old male child, a product of nonconsanguineous marriage and resident of Karachi, was diagnosed to have XP; he had multiple growths on his lip, eyelids, face, nasolabial, and shoulder at different times since 2015, and all of them were resected. He had a complaint of swelling in the eye for 2 months. Magnetic resonance imaging (MRI) orbit shows a subcutaneous soft tissue lesion in the right eyelid. A computed tomography (CT) scan showed a redemonstration of a large mass lesion (3.4 cm) in the right orbital cavity with significant involvement and distortion of the right globe with possible involvement of the lacrimal gland. Multiple small subcentimeter-sized bilateral levels I, II, and III cervical lymph nodes are noted as detailed was seen. A biopsy of the orbital mass was done and showed well-differentiated

Table 1 Cases summary

	Age/Sex	Consanguineous marriage	Family history	Manifestation	Histopathological findings	Treatment
Case 1	5 y/M	–	–	Eruption on his forehead	Squamous cell carcinoma, acantholytic type	Underwent a scalp lesion excisional biopsy
Case 2	6 y/M	Yes	Yes	Multiple skin nodules for 2 years	Keratinizing squamous cell carcinoma	Wide-margin excision of the scalp was done; the lesion was completely excised
Case 3	14 y/M	Yes	–	Swelling in the right eye that gradually increased in size and becomes ulcerated for 3 months	Keratinizing squamous cell carcinoma	His surgery was done at another medical facility
Case 4	11 y/M	No	–	Swelling in the eye for 2 months; a biopsy of the orbital mass was done	Squamous cell carcinoma	Patient has locally extensive disease with lymphadenopathy referred for excision
Case 5	10 y/F	Yes	Yes	Swelling inside the right eye for 1 year; eye conjunctival lesion was done	Squamous cell carcinoma	She just came to us for a workup
Case 6	9 y/M	Yes	Yes	Multiple lesions were observed from the right side, left side of the forehead, and left eye lateral to the lateral canthus	Basal cell carcinoma	Biopsy from the left forehead pigment lesion was done
Case 7	13 y/M	Yes	Yes	Multiple ulcerating lesions on his face	Basal cell carcinoma	Wide margin excision was done for a mass protruding from the nostril
Case 8	10 y/M	Yes	–	Fleshy outgrowth in the left eye for 1 month	Squamous cell carcinoma	Incisional biopsy of left conjunctival mass
Case 9	7 y/F	Yes	–	Red raised eroded nasal lesions for the past 5 years progressively	Squamous cell carcinoma + basal cell carcinoma	Wide-margin excision was done

squamous cell carcinoma; disease was in poor prognosis and patient was referred to dermatologist and plastic surgeons.

Case 5

A 10-year-old female child, the first offspring of a consanguineous marriage, and a resident of Mirpur Mathelo, Sindh, presented with a history of dry scaly skin since the age of 2 months, and swelling inside the right eye for 1 year. His one brother and one sister have the same skin condition. The first biopsy of the right eye conjunctival was done in March 2020 at a local hospital and reported moderate dysplasia with foci suspicion of invasion. They diagnosed her with XP with the suspicion of squamous cell carcinoma. She came to us in November 2020 where a biopsy of her right eye conjunctival lesion was performed, and it revealed that conjunctival tissue was lined by stratified squamous epithelium, and infiltration of neoplasm was seen in the deeper stroma. Adjacent stroma had dense acute and chronic inflammation with dilated and congested blood vessels. Immunohistochemical stain K_i-67 highlighted the increased proliferation in neoplastic cells. She just came to us for a workup.

Case 6

A 9-year-old male patient, resident of Larkana and the product of a consanguineous marriage, was a known case of XP. Physical examination of the face, eyes, lips, and neck demonstrated hypopigmented and hyperpigmented macules, dry skin, a blister on the face, and extreme sensitivity to sunlight. His one brother died of a similar skin condition. According to their parents, he developed swelling on the forehead 1 month back; they went to the local hospital where he was given multiple antibiotics but the swelling did not resolve. They came to our hospital, and multiple lesions were observed from the right side, left side of the forehead, and left eye lateral to the lateral canthus. The biopsy from the left forehead pigment lesion showed BCC (►**Fig. 1C**). The biopsy from the lateral to left eyebrow and lateral canthus showed a small fragment of skin tissue with extensive ulceration, marked cautery artifacts, and focal dysplastic squamous epithelium.

Case 7

A 13-year-old boy, a resident of Larkana and the product of a consanguineous marriage, was a known case of XP. He came

with the complaint of pigmented lesions all over the body at 4 months of age and ulceration on the nose for the last 1 year. His one sibling died at the age of 9 from skin cancer. The patient was under treatment at a local hospital since birth for different multiple ulcerating lesions on his face that were then grafted with the skin of his arm and leg as well. He had been operated on for a mass protruding from the nostril which was diagnosed as BCC.

The patient was referred to us for a similar lesion of the face because of nonaffordability. On examination, the patient was vitally stable and had eroding lesions at the tip of the nose. Wide margin excision was done for 1.5 cm lesion at the tip of the nose and full-thickness skin involvement. Dermal upper lip of 1.2 cm was involved. Nose and lip lesions were excised; both lesions showed BCC. The patient was on follow-up and stable.

Case 8

A 10-year-old male child, resident of New Dero (Larkana) and the product of a consanguineous marriage, referred to our hospital with a known case of XP. He came with the complaint of fleshy outgrowth in the left eye for 1 month. MRI neck plain and contrast were done that showed thickening of the anterior aspect of the left globe noted with abnormal signals 2.7 cm on axial sections. Incisional biopsy of left conjunctival mass (13.1.2022) revealed poorly differentiated squamous cell carcinoma. Immunohistochemical markers were performed where CK5/6, p63, and p40 were positive in neoplastic cells.

Again biopsy was done in march 2022 of left orbital exenteration; the tumor was seen in the conjunctiva that extends to the sclera, and the finding was consistent with the poorly differentiated squamous cell carcinoma. Immunohistochemical markers were performed showing that CK5/6 and p40 were positive in neoplastic cells, while HMB-45 was negative in neoplastic cells. The patient was in regular follow-up with the dermatological team.

Case 9

A 7-year-old female, resident of Jamshoro, the product of consanguineous marriage, and a known case of XP, presented with a complaint of red raised eroded nasal lesions for the past 5 years which was progressively increasing. The radiological test was performed: A brain CT showed mucosal thickening at the left maxilla. A CT of the neck showed ill-defined subcutaneous soft tissue thickening at the left cheek and subcentimeter cervical lymph nodes were also seen. Wide-margin excision was done on the right cheek lesion, chin skin lesion, left eyebrow lesion, and left cheek lesion. Multifocal BCC and squamous cell carcinoma were diagnosed simultaneously on the right cheek lesion and chin skin lesion. Wide margin excision on left eyebrow lesion showed nodular BCC (►**Fig. 1D**).

Discussion

XP is an uncommon hereditary condition characterized by high photosensitivity, which produces skin pigmentation with an increased risk of developing skin cancer.[11] Due to consanguineous marriages, XP is significantly more frequent in the Middle East.[12] Consanguinity was discovered in seven of our cases, which is consistent with examples described in West Africa.[1] The cutaneous malignancies appeared at an average age of 9 years in our study, which was in concordance with Kraemer et al, who reported an average age of 8 years.[12]

Here, we reported nine cases of xeroderma pigmentosa, in which three cases showed the severe photophobia as two cases showed keratinizing squamous cell carcinoma and one case repesented with extreme photosensitivity, with no significant neurological abnormalities. The diagnosis was done on the clinical and histopathological findings, while in some cases immunophenotyping was also done. The difficulty of diagnosis occurred in some cases. For example, smaller biopsy with limited excision was done in cautery artifact lesions close to the eye area.

In XP, the development of malignant skin tumors is a leading cause of morbidity and mortality.[13] A survey of the literature found that there is no uniform distribution rate of malignant tumors among XP patients.[14–16] Even though BCC is more prevalent in certain prior studies,[17,18] we have only reported two cases of BCC. A study by Baykal et al reported six cases of BCC.[11] While the most common malignant skin tumor was reported to be squamous cell carcinoma in a review article that included 830 published XP cases from 1874 to 1982[12] and in other several studies, they also reported squamous cell carcinoma was the commonest[19,20] which was in agreement with our study because we reported six cases of squamous cell carcinoma. We also reported one unusual case having both skin malignancies (squamous cell carcinoma and BCC). Melanoma was reported in many studies,[11,13] but we did not find melanoma in our patients. We have reported all the lesions and masses on the face (eye, nose, chin, cheek, and forehead) and scalp in all patients. Five patients had lesion on eyes: three (60%) had lesion on orbital region, one (20%) had conjunctival growth, and one (20%) had a lesion on an eyebrow. The conjunctival abnormality was also reported by Mulimani et al.[21]

This study had some limitations, one of which is the small number of patients. From our study, we inferred that early detection, prevention, and regular follow-up with a dermatologist and ophthalmologist are essential for treating the condition and minimizing its symptoms. The use of strict sun protection such as special spectacles and sunscreen lotions and avoidance of the sun are all key steps in preventing skin cancer and enhancing the quality of life and life expectancy of XP patients. The prognosis for XP is generally favorable in the absence of neurological abnormalities and circumstances when it is detected early.

However, protection against sunlight and UV radiation is crucial. If it is possible, a genetic counseling and prenatal diagnosis are suggested. The authors recommend that more research be done on the XP epidermal stem cell and DNA repair.

Funding
None.

Conflict of Interest
None declared.

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Bilateral CMV Retinitis in a Patient with Relapsed Non-Hodgkin Lymphoma on Oral Metronomic Chemotherapy: Case Report and Review of Literature

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Ind J Med Paediatr Oncol 2025;46:104–108.

Abstract

Cytomegalovirus (CMV) retinitis is one of the common complications in profoundly immunosuppressed patients such as those with acquired immune deficiency syndrome. It has been rarely reported in patients with lymphoma on aggressive chemotherapy. We encountered a patient with bilateral CMV retinitis who developed this vision-threatening complication while on low-dose palliative metronomic chemotherapy with oral drugs (cyclophosphamide, procarbazine, etoposide, and prednisolone). Though the infection resolved with treatment, there was residual vision loss. This case is presented to sensitize clinicians to the possibility of unusual infections in patients on long-term oral chemotherapies.

Keywords
- case report
- lymphoma
- oral metronomic chemotherapy
- cytomegalovirus
- retinitis

Introduction

Oral metronomic chemotherapy (OMCT) is often used in patients with relapsed lymphomas. The toxicities of OMCT are generally lower than those of intravenous chemotherapy, making it a preferable option in patients with advanced disease or poor general condition. However, prolonged use of OMCT can lead to immunosuppression and result in unusual infections.[1] Here we describe a rare case of bilateral cytomegalovirus (CMV) retinitis in a patient with relapsed Non-Hodgkin Lymphoma on OMCT.

Case Report

In 2014, a 52-year-old gentleman with no comorbidities with grade 1, stage IV follicular lymphoma achieved complete response after six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy. He relapsed in 2017, and lymph node biopsy was suggestive of diffuse large B cell lymphoma. He was treated with rituximab, cyclophosphamide, epirubicin, vincristine, prednisolone (R-CEOP) as he was unwilling for high dose chemotherapy or stem cell transplantation. After five cycles

article published online
April 26, 2022

DOI https://doi.org/10.1055/s-0042-1742614.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of R-CEOP, he developed a persistent headache. The MRI brain was within normal limits, but the cerebrospinal fluid analysis showed lymphomatous involvement. He was unwilling for any intensive treatment and was started on OMCT with the PEP-C regimen comprising of prednisolone 20 mg once daily for 14 days, etoposide 50 mg once daily for 28 days, procarbazine 50 mg once daily for 28 days, cyclophosphamide 50 mg once daily for 28 days, and triple intrathecal therapy comprising of inj. methotrexate 12 mg, inj. cytarabine 30 mg, and inj. hydrocortisone 15 mg.[2] His symptoms improved significantly after two to three cycles of OMCT. CSF cytology became negative for malignant cells after four cycles of OMCT, and the contrast-enhanced CT scan of the chest, abdomen, pelvis showed no evidence of systemic disease.

In 2019, after 13 courses of PEP-C regimen, he presented with acute onset, painless diminution of vision in both the eyes—right eye (RE) more than the left eye (LE). Visual acuity was hand movements in RE and 6/18 in LE. Fundus examination in both eyes revealed scattered whitish lesions on the retina suggestive of retinitis, along with superficial retinal hemorrhages and perivascular exudates involving the major retinal vessels. The lesions involved the macular center in the RE while the same was spared in the LE (►**Fig. 1**). There was no associated vitritis. The differential diagnoses considered were intraocular lymphoma and CMV retinitis. The vitreal aspirate was positive for CMV DNA (deoxyribonucleic acid) PCR (polymerase chain reaction) and negative for malignant cells on cytology. The peripheral blood CMV DNA PCR was positive; however, there were no symptoms of disseminated CMV infection. He had no chest or gastrointestinal symptoms; chest X-ray and LFTs were normal. Thus, there was no evidence of systemic CMV infection. HIV serology was negative. He was managed with intravitreal ganciclovir (2 mg/0.1 mL, weekly once, six doses for each eye) and intravenous ganciclovir (10 mg/kg in two divided doses daily for 1 month). This was followed by oral valganciclovir 900 mg twice daily for 21 days and once daily for 2 months. Gradually, the retinal lesions resolved and manifested healing. CMV DNA PCR of the blood or vitreal aspirate was not repeated, and the disappearance of the retinal vascular sheathing was taken as a marker of clinical improvement. The visual acuity in the RE improved to counting fingers while the LE vision improved to 6/9. OMCT was discontinued as the relapsed lymphoma had shown complete clinical and radiologic response. The patient is currently on follow-up and is alive and well 2 years after the event.

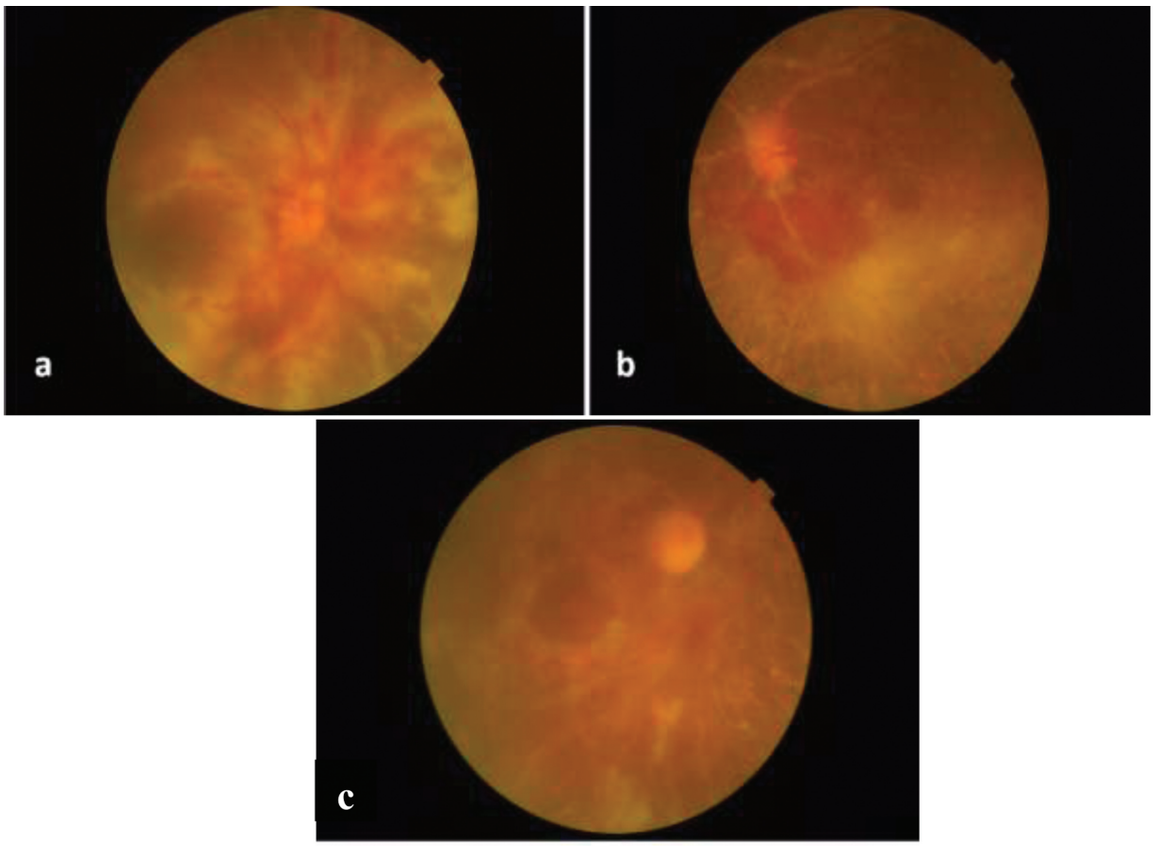

Fig. 1 Funduscopic images of both eyes at presentation. Fundus images showing (**a**) right eye: white retinitis lesions with retinal hemorrhages and perivascular sheathing with involvement of the optic disk and the macula; (**b**) Left eye: white retinitis lesions with retinal hemorrhages and perivascular sheathing with involvement of infero-temporal retinal quadrant and sparing of the center of the macula; (**c**) image of the right eye after 2 months showing improvement in retinal hemorrhages and perivascular sheathing.

Table 1 Case reports of cytomegalovirus retinitis in patients treated for lymphoma

Sl no	Author (Ref)	Lymphoma subtype	Chemotherapy	Diagnosis	Treatment given for CMV retinitis	Visual outcome
1.	Smith[15]	HL	MP	Inclusion body bearing cells (post-mortem)	NR	Patient died
2.	Nasir and Jaffe[16]	HL	MOPP-ABVD	Vitreous biopsy and CMV DNA PCR	IV gan f/b IV foscarnet	Improved
3.	Toy and Knowlden[17]	HL (R)	Chl-VPP	Inclusion body bearing cells (post-mortem)	Post mortem diagnosis	Patient died
4.	Tudesq et al[18]	HL (R)	BV	Vitreous humor aspirate and CMV DNA PCR	IVtr and IV Gan f/b PO Valgan	NR
5.	Tyagi et al[19]	B-NHL	R-CHOP	Vitreous biopsy and CMV DNA PCR	IVtr and IV Gan f/b PO Valgan	Improved left eye: Total visual loss
6.	Kang[20]	DLBCL	R-CHOP	Vitreous aspirate and CMV DNA PCR	IVtr and IV Gan	Improved
7.	Kawai et al[21]	AITL	CHOP	Peripheral blood CMV DNA PCR	IVtr and IV Gan	Improved
8.	Chawla et al[22]	NHL	CHOP	Vitreous biopsy and CMV DNA PCR	Observation	Stable disease
9.	Akpek et al[23]	NHL	NR	Diagnostic vitrectomy and CMV DNA PCR	IV gan	Bilateral visual loss
10.	Vote et al[24]	PSPL	Splenectomy, CHOP	Vitreal aspirate and CMV DNA PCR	IV gan f/b IV foscarnet	Stable
11.	Derzko et al[25]	DLBCL (R)	Alemtuzumab, Fludarabine	CMV DNA PCR of vitreal fluid	IV gan and foscarnet	Did not improve
12	Reddy et al[26]	NHL	Various chemotherapy	CMV DNA PCR of vitreal fluid	IVtr, IV Gan and PO Valgan	Improved
13	Current patient	DLBCL	PEP-C oral	CMV DNA PCR of vitreal aspirate	IVtr, IV Gan f/b PO Valgan	Improved

Abbreviations: (R), relapsed disease; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AITL, angioimmunoblastic T-cell lymphoma; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; CVPP, chlorambucil, vinblastine, procarbazine, prednisolone; DLBCL, diffuse large B cell lymphoma; DNA, deoxyribonucleic acid; FL, follicular lymphoma; Gan, ganciclovir; HL, Hodgkin lymphoma; IV, intravenous; IVtr, intravitreal; MOPP/ABVD, mechlorethamine, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin, vinblastine, dacarbazine; MP, mechlorethamine, prednisolone; NHL, non-Hodgkin lymphoma; NR, not reported; PCR, polymerase chain reaction; PO, peroral; PSPL, primary splenic plasmacytoid lymphoma; Valgan, valganciclovir; PEP-C, oral procarbazine, etoposide, prednisolone, and cydophosphamide; CMV, Cytomegalovirus; DNA, Deoxyribonudeic acid.

Discussion

Our patient had relapsed lymphoma and was on chronic low dose chemotherapy with potential for immune suppression. There were two primary differential diagnoses. One was lymphomatous involvement of the eye, considering the earlier history of meningeal involvement. The second was infectious retinitis, e.g., CMV, toxoplasmosis, candida, pneumocystis, varicella-zoster, and herpes simplex infections.[3] Intraocular lymphoma usually presents as chronic posterior uveitis involving the vitreous (increased haze and cellularity). Additionally, retinitis (perivascular yellowish-white retinal infiltrates and intraretinal hemorrhages) and retinal vasculitis (sheathing of blood vessels) may ensue.[4] CMV retinitis can closely mimic the retinal presentation of intraocular lymphoma.[5] CMV retinitis is seen in 5 to 20% of patients undergoing solid organ transplantation and in 15 to 30% of those undergoing allogeneic hematopoietic stem cell transplantation.[6,7] It presents as focal, perivascular retinal whitening with or without intraretinal hemorrhages and progresses in centrifugal or "brushfire" pattern. It can progress to full-thickness retinal necrosis and retinal detachment.[6] In this patient, the diagnosis was established by detecting CMV DNA PCR of the vitreal aspirate.

CMV serology cannot be used as the sole diagnostic investigation as it can be positive in 80 to 90% of the general population in India.[8] The gold standard of diagnosis is the isolation of the virus in culture—however, CMV culture is challenging. It takes a long time and is falsely negative in 50% of cases.[9,10] On the contrary, DNA amplification techniques (PCR) from blood or vitreal aspirate provide a timely diagnosis with high sensitivity and specificity.[11,12] CMV retinitis is vision-threatening, and treatment has to be instituted as soon as the diagnosis is established. Intravitreal treatment is

vital in vision-threatening disease (central lesions <1,500 µm from the fovea or closer to the optic nerve head). However, systemic anti-CMV treatment cannot be avoided. One-third of the patients treated with intravitreal therapy alone develop extraocular CMV disease and contralateral retinitis.[13] Hence, a combination of intravitreal plus systemic therapy is preferred as was used in our patient. When the disease is not immediately vision-threatening, systemic therapy can be used (IV ganciclovir, IV foscarnet, IV cidofovir, and oral valganciclovir) without intravitreal treatment. Patients are to be monitored with indirect ophthalmoscopy weekly/once in 2 weeks while on induction therapy and monthly till the completion of anti-CMV treatment.[14]

Several cases of CMV retinitis in patients with lymphoma have been described (►**Table 1**). Most cases developed in patients on aggressive chemotherapy regimens, which are more likely to produce myelosuppression and immune suppression. Unfortunately, limited data are available regarding risk of CMV relapse while salvaging further relapses. One of the options is to continue chemotherapy with close monitoring of CMV DNA, as is done in the context of an allogeneic transplant. The other option is to avoid immunosuppressive regimens which are heavy on steroids. Our report is the first one describing CMV retinitis during OMCT. The strength of our study is that it highlights that CMV infection is a rare but serious complication of a seemingly less intensive treatment like oral metronomic chemotherapy. The weakness is that we do not have information on the immune status of the patient, like the CD4 counts or immune globulin levels.

Conclusion

Despite low doses, long-term use of cyclophosphamide and prednisolone possibly induces a chronic immunodeficiency state making the patients susceptible to rare infections. This case is presented to alert clinicians about unusual but severe infections in patients on OMCT.

Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

None.

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B-Lymphoblastic Leukemia Presenting with an Isoderivative Philadelphia Chromosome—A Rare Case Report and Review of Literature

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Ind J Med Paediatr Oncol 2025;46:109–113.

Abstract

The Philadelphia chromosome is seen in 5% of pediatric and 25 to 50% of adult cases of acute lymphoblastic leukemia (ALL). It is linked to aggressive illness with a dismal prognosis. Additional chromosomal abnormalities are not prevalent with translocation 9;22; nevertheless, isochromosome derivative [ider(22)] with this translocation is rarely recorded in the literature. This is the third instance of ider(22) in pediatric B-cell acute lymphoblastic leukemia (B-ALL). Bone marrow chromosome analysis by G-banding showed 46,XX,t(9;22)(q34;q11.2)[6]/46,XX,ider(22)(q10)t(9;22)(q34;q11.2)[14]. Fluorescence in situ hybridization (FISH) analysis for *BCR::ABL1* fusion showed 40% of interphase cells with two and 35% with three fusion signals that were in concordance with the karyotype. The patient was categorized as National Cancer Institute (NCI) high-risk (HR) and started with HR chemotherapy according to Children's Oncology Group (COG) protocol. Postinduction remission assessment by flow cytometry showed 2.6% measurable residual disease. The case highlights significance of cytogenetic analysis despite availability of advanced techniques like FISH. The prognostic significance of concurrent ider22(q10) with t(9;22) is yet to be explored.

Keywords
- acute lymphoblastic leukemia
- immunophenotyping
- Philadelphia chromosome
- cytogenetic analysis
- measurable residual disease

Introduction

Philadelphia (Ph) chromosome is less often found in B-cell acute lymphoblastic leukemia (B-ALL) patients; however, it is commonly (90–95%) present in chronic myeloid leukemia (CML) patients.[1,2] Ph chromosome can be detected in about 25% of adult ALL and only 2 to 4% of pediatric ALL.[1,3] Presence of double Ph chromosome is infrequent in ALL but reported in some cases of CML during the blast crisis phase.[4] When compared to Ph chromosome-negative ALL, Ph chromosome-positive ALL is typically associated with a more aggressive disease that may be more resistant to treatment and can have a poorer prognosis compared to other types of pediatric ALL.[1,5] Currently, the mainstay of treatment is a tyrosine kinase inhibitor plus intensive chemotherapy, followed by hematopoietic stem cell transplant (HSCT) after the first remission.[6] We report a rare case of a 4-year-old girl diagnosed as a case of isoderivative Ph chromosome-positive B-ALL. This chromosomal aberration is exceptionally rare in B-ALL. The case is being reported to spread awareness about significant additional cytogenetic findings in a case of B-ALL with recurrent cytogenetic abnormalities. This patient also revealed other poor clinical features like hyperleukocytosis at the time of presentation and did not achieve postinduction remission.

article published online
July 5, 2023

DOI https://doi.org/10.1055/s-0043-1770094.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Case Report

A 4-year-old girl presented to emergency department of pediatric oncology unit with a history of recurrent epistaxis for 2 months and was severely anemic. There is no significant history of any past illness and/or genetic disease in the family. On general physical examination, she had lymphadenopathy and hepatosplenomegaly.

Differential Diagnosis, Investigations, and Treatment

Complete blood count showed hyperleukocytosis with white cell count of 153×10^9/L, anemia with hemoglobin of 7.5 gm/dL, and thrombocytopenia with a platelet count of 18×10^9/L. Blood film showed a leucoerythroblastic picture with 84% blasts. Immunophenotyping performed on peripheral blood using 8-color flow cytometry (BD FACS Canto II) revealed the following immunophenotypic profile:

- Positive for CD34, CD45, CD19, CD79a, CD20, CD10, CD66, CD9 and CD58
- Negative for intra-cytoplasmic CD3, intra-cytoplasmic MPO, CD13, CD33

On the basis of flowcytometry, the case was diagnosed as B-ALL (►**Fig. 1**). Other laboratory investigations including liver and kidney function tests were within normal range; however, serum albumin was low (2.0 g/dL). The diagnostic lumbar puncture for central nervous system (CNS) infiltration showed CNS1 status that is consistent with absence of blasts. Bone marrow specimen was received for fluorescence in situ hybridization (FISH) and cytogenetic analysis by G-banding (►**Fig. 2**). Interphase FISH revealed atypical signal pattern, comprised of three fusion signals that were further evaluated by metaphase FISH (►**Fig. 2B–D**). FISH analysis of the bone marrow for *BCR::ABL1* dual color dual fusion probe using Leica Biosystems automated cell imaging system (CytoVision) detected 70% of *BCR::ABL1* fusion with 35% of those cells harboring three fusion signals, indicating the presence of extra Ph chromosome. Karyotype analysis revealed the presence of an abnormal female chromosome complement comprised of two related cell lines. The first cell line (stem line) was seen in six cells with a Ph chromosome derived by a balanced translocation between the long arms of chromosomes 9 and 22. The second cell line (side line) is seen in 14 cells with an isochromosome for the long arm of chromosome 22 resulting by t(9;22; ►**Fig. 2A**) These findings were consistent with FISH results. Translocation (9;22) results in the fusion of the *ABL1* gene at 9q34 and the *BCR* gene at 22 q11.2 that is associated with poor prognosis in B-ALL. The presence of *ider(22)* is very uncommon in pediatric B-ALL. She was categorized as NCI high-risk and received modified COG protocol along with Tyrosine kinase inhibitor (TKI).

Outcome and Follow-Up

Postinduction bone marrow aspirate on morphological review showed remission; however, measurable residual disease assessment by flowcytometry showed 2.6% residual disease. A HSCT was not possible due to financial constraints;

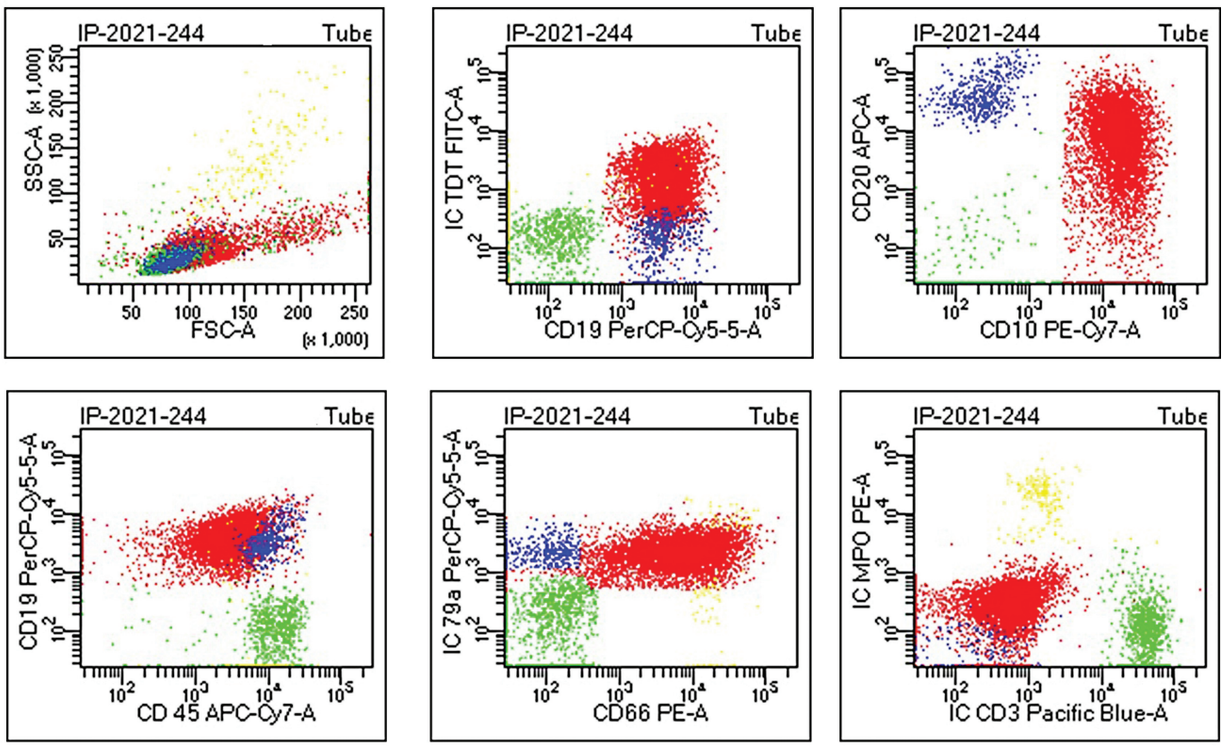

Fig. 1 Flow cytometry showing positivity for Tdt, CD19, CD10, CD20, CD45, CD79a, CD66 (color code: red = blasts, blue = B-lymphocytes, green =T-lymphocytes, yellow = granulocytes).

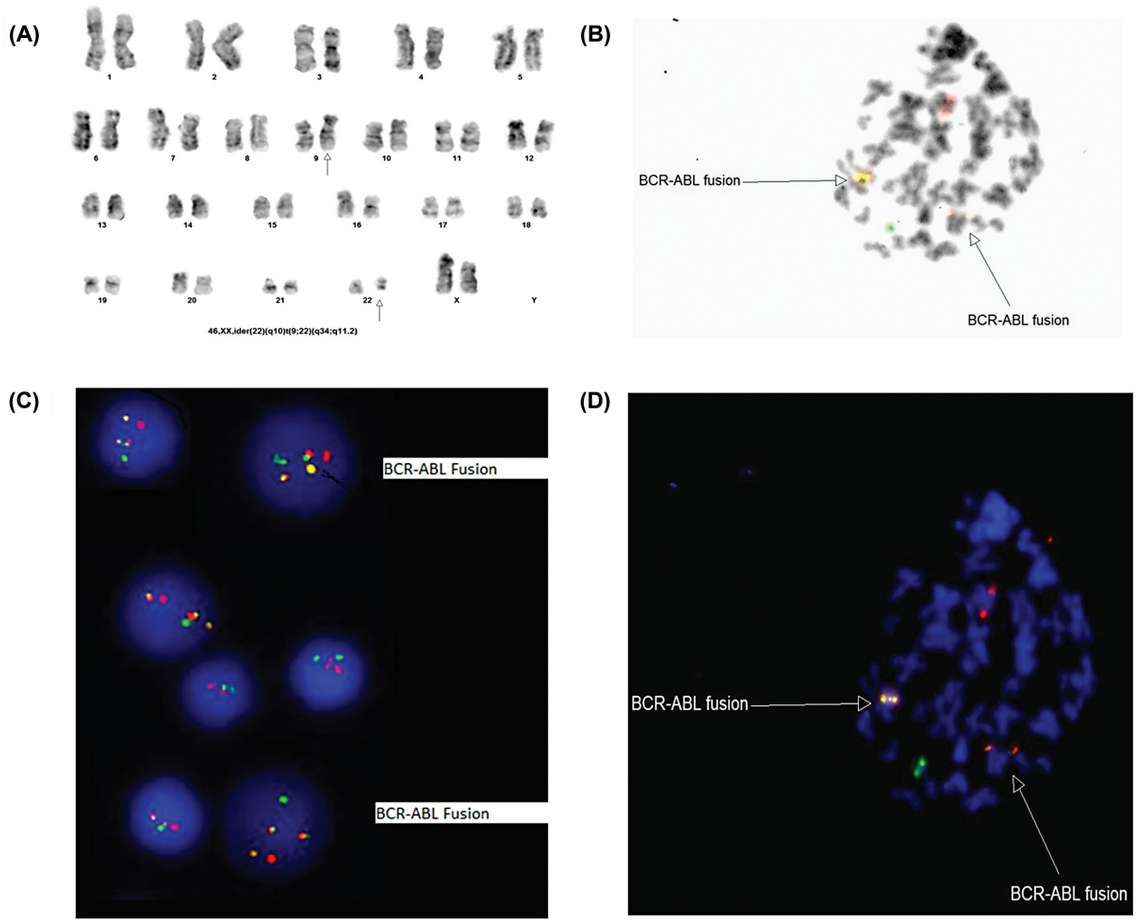

Fig. 2 (**A**) Karyotype, (B) met FISH with inverted 4'6-Diamidino-2-phenylindole (DAPI), and (C) interphase fluorescence in situ hybridization (FISH), (**D**) met FISH.

therefore, chemotherapy was adjusted accordingly. Currently, she is on high-risk consolidation chemotherapy.

We have summarized the features of our study case and other published cases in ►**Table 1.**

Discussion

Despite recent advancement in molecular techniques, several multicenter studies still emphasize significance of cytogenetic studies in determining prognosis of numerical and structural aberrations in hematological neoplasms. Chromosome analysis at the G-band level is still the most important investigation in B-ALL.[7] FISH techniques are used to identify specific structural aberrations that played a vital role in risk stratification of B-ALL and have been implicated in all treatment protocols.[8] But FISH has its own limitations due to targeted technique that does not help in identifying whole genetic makeup of an individual.

Acute leukemia with *BCR::ABL1* is currently classified as high-risk subgroup that requires intensive chemotherapy to achieve optimum response in terms of hematological remission. Few cases were reported with isochromosome 9 with Ph+ in pediatric ALL patients.[9–12] However, the isochromosome of the long arm of derivative chromosome 22 from t (9;22) with a deletion of 22p, ider(22)(q10)t(9;22) is very rare. To the best of our knowledge, this is the third case of ider (22) in B-ALL; the first case was reported by Yamamoto et al and the second case was of an adult woman with ider(22) with Ph+ B-ALL was reported by Meza-Espinoza et al.[13,14]

Yamamoto et al[13] reported the first case of ider(22) chromosome in acute leukemia similar to this case. U-type sister chromatid exchange is the probable hypothesis behind ider(22) chromosome formation. The ider(22) chromosome is pathologically considered equivalent to the presence of double Ph chromosome, which is the most frequent additional aberration in such cases, known to be one of the main secondary chromosomal changes related to the clonal evolution of cells with t(9;22).[15]

Concomitantly with clonal divergence, this patient was presented with hyperleukocytosis that is also an established poor prognostic factor. CNS infiltration was not observed in this case but despite intensive chemotherapy along with timely administration of TKI, she could not achieve post-induction remission. Reported cases with ider(22) showed frequent involvement of CNS by leukemic cells at the time of diagnosis.[14]

These cases are evidence of clonal evolution in B-ALL and warrant complete cytogenetic studies in all patients to

Table 1 Features of our case study and published cases with ider(22)

Studies	Age/ Sex	Clinical features	G-banding or FISH Analysis	Treatment	Outcome
Ramachandran et al (2016)[16] *Patient 1*	29y/M	Massive splenomegaly	46,XY,der(9)t(9;22)(q34.13;q11.23), ider(22) (p12)t(9;22)[7]/47,sl, +ider(22)[21]/48,sdl, +ider(22)[2]	IM 400 mg daily (8.5 years)	BM study revealed 8% blasts, suggestive of CML-CP. The patient was started on second line TKI, dasatinib, and attained hematological remission 1 month later; now he is on dasatinib for 2 months
Patient 2	51y/M	Moderate splenomegaly	46,XY,t(9;22)(q34.13;q11.23)[4]/ 46,−der(22)t(9;22), +ider(22)(p12)t(9;22)[4]/47,sdl1, +ider(22)[13]/48,sl, +der(22), +ider(22)[4]/47,sl, +8[5]	IM 400 mg daily (6 months)	Initially responded, but subsequently lost the hematologic response. Switch to second line TKI, dasatinib
Meza-Espinoza et al (2016)	54y/F	–	46,XX,t(9;22) (q34;q11.2)[3]/46, idem,ider(22)(22pter→ 22q11.2::9q34→9q? tel::9q?tel→ 9q34::22q11.2→22pter)[14]/46, idem,t(13;17) (q14;q25)[3]/46, idem, + 1,dic(1;1)(?;?), t(13;17)(q14;q25) [8]/46,XX[1]	Received vincristine, prednisone, and daunorubicin-based chemotherapy	04 months later, the patient died after infiltrations were detected both to the retro-ocular and central nervous systems
Our study	4y/F	Lymphadenopathy and hepatosplenomegaly	46,XX,ider(22)(q10)t(9;22)(q34;q11.2)	She was categorized as NCI high-risk and received modified COG protocol along with imatinib	Postinduction bone marrow aspirate on morphological review showed remission however measurable residual disease (MRD) assessment by flowcytometry showed 2.6% residual disease

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; CP, chronic phase; FISH, fluorescence in situ hybridization; IM, imatinib; TKI, tyrosine kinase inhibitor.

determine any high-risk factor. According to published literature, relapse is common in cases with additional cytogenetic aberrations in B-ALL.[13]

Availability of complete diagnostic profile and timely workup of this case played a significant role in the management of this patient. The findings were further verified by metaphase FISH in parallel. Tyrosine kinase inhibitor inhibitor was timely added to her B-ALL protocol. However, HSCT could not be offered as the said facility is not currently available in our unit and they could not get it done privately due to financial constrain. Owing to the dismal outcome of chemotherapy in these patients, HSCT is the treatment of choice. Polymerase chain reaction is the recommended modality to monitor molecular response in these patients that should be incorporated in such cases. Monitoring for genetic evolution and molecular response are the future perspectives to impact the outcome of these patients.

Conclusion

We highlight the significance of cytogenetic aberrations in pediatric B-ALL patients. Further studies are needed to provide insight into this rare subgroup and understand the disease course of these patients with newer therapeutic protocols.

Authors' Contributions

Neelum Mansoor is involved in the study of concept and design. Syeda Ambareen Zehra did the acquisition of data. Sidra Maqsood drafted the manuscript. Imad Bakri was involved in the critical revision of the manuscript for important intellectual content. Sidra Maqsood and Syeda Ambareen Zehra are involved in administrative, technical, and material support. Neelum Mansoor supervised the study.

Patient Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We offer our sincere thanks to Mr. Talha Israr and Mr. Azfar Ahmed, assistant managers in department of hematology (IHHN) for their contribution.

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Chemotherapy-Induced Fingerprint Effacement Leading to Deprivation of Health Insurance: A Case Series and Review of Literature

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Ind J Med Paediatr Oncol 2025;46:114–118.

Abstract

Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PMJAY) is a game changer for the Indian health care system, where patients with cancer are the major beneficiaries. Some intrinsic procedural shortcomings are restricting the beneficiaries to utilize it optimally. We report a case series of patients receiving chemotherapy who had developed adermatoglyphia because of chemotherapeutic treatment. Therefore, these patients became ineligible for getting the benefits of PMJAY, because of failure of the biometric system to recognize their fingerprints. Hence, patient treatment could not be completed. As a solution, we suggest that the alternatives to fingerprint recognition like face recognition and iris scanning be incorporated into the biometric system to ensure continuous benefit of PMJAY to such patients.

Keywords
- PMJAY
- fingerprints
- cancer
- chemotherapy
- Ayushman Bharat

Introduction

Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PMJAY) was launched by the Indian government to ensure health care services worth Rs. 500,000 per family per year for the poor and vulnerable population (~50 million).[1] According to GLOBOCAN-2020 estimates, nearly 1.3 million new cases of cancer were diagnosed in India during the year 2020.[2] Among all the specialties covered by PMJAY, patients with cancer receive the greatest benefit. Nearly 700,000 chemotherapy procedures have been performed under this scheme since 2018.[3] Access and adherence to cancer care services have improved with this program, and will eventually lead to a reduction in cancer-related deaths in India. Before every chemotherapy procedure, patients go through a verification process of fingerprint recognition and Aadhaar card verification to be eligible for PMJAY benefits. Unfortunately, adermatoglyphia is anticipated to occur in nearly 40% of certain subsets of patients with cancer, causing them to lose their fingerprints after the start of chemotherapy.[4]

We describe a series of patients who received chemotherapy under the PMJAY for different malignancies and developed adermatoglyphia because of chemotherapy. Premature loss of the fingerprint caused the failure of the verification system to authenticate their procedures. Hence, they could not get the benefit of chemotherapy treatment under the PMJAY scheme, leading to disease progression. We noticed that this condition also affects their ability to use their digital gadgets such as smart phones that commonly require fingerprint verification to lock or unlock them. This can cause additional distress as it affects their independence and daily routines.

article published online
November 25, 2024

DOI https://doi.org/10.1055/s-0044-1795094.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Thus, Adermatoglyphia may not only deprive patients of health insurance benefits but also hinder their use of everyday technology. In this case series, following ethical committee waiver and patient consent, we describe the cases of four patients who were unable to receive chemotherapy under the PMJAY scheme. This was because, due to their adermatoglyphia, the fingerprint scanner was unable to authenticate their identity before a chemotherapy procedure- a routine process before admission under PMJAY- which leads to disease progression in the absence of treatment.

Case Report

Case 01

A 19-year-old man presented with a large mass in the left cervical region and the left lung apex that involved the extraparenchymal lung tissue with an erosion of the C7, D1, and D2 vertebrae and the scapula. He was diagnosed with Ewing's sarcoma in August 2022. He was started on the VAC (vincristine, doxorubicin, and cyclophosphamide) drug regimen. He completed four cycles of chemotherapy and was responding well. However, his PMJAY card registration eventually failed, because the biometric system could not recognize his fingerprints (►**Fig. 1a**). On examination, his fingerprints were not elicitable due to chemotherapy, with other potential causes being ruled out. Therefore, he could not be admitted for further treatment. However, his treatment was eventually resumed after a delay of 1 month. With crowdfunding and nongovernmental organization (NGO) support, he was able to complete 13 palliative chemotherapy cycles of VAC without PMJAY support.

Case 02

A 27-year-old man presented with complaints of abdominal pain and obstruction in November 2022. On evaluation, he was diagnosed with adenocarcinoma of the right colon and underwent laparotomy with right hemicolectomy. The post-op histopathology was suggestive of adenocarcinoma of the right colon (pT3N1M0). He was planned for adjuvant chemotherapy (FOLFOX regimen). Nevertheless, after completion of five cycles, his PMJAY card registration failed because his fingerprints were not recognized by the biometric system (►**Fig. 1b**). The remaining cycles were completed with NGO support.

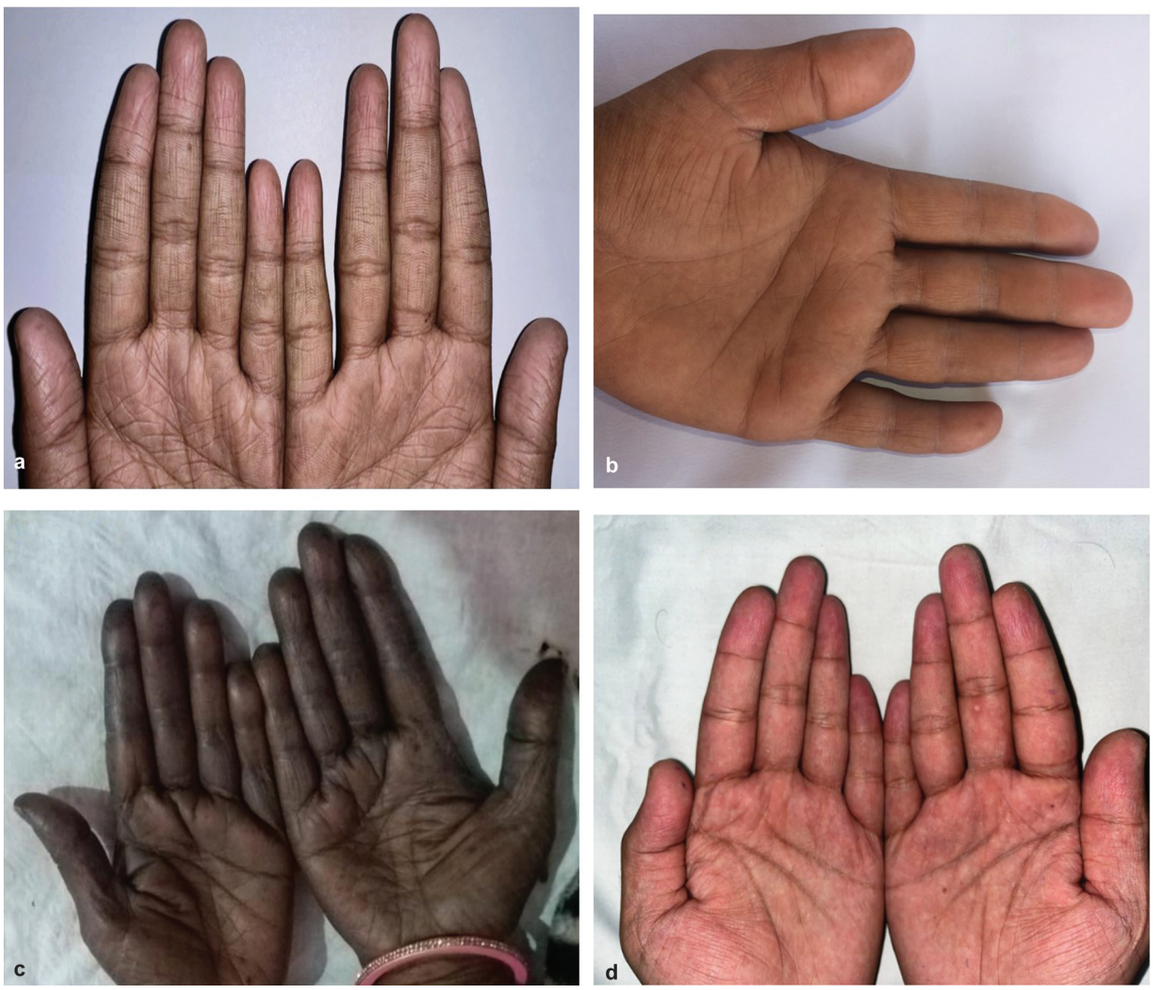

Fig. 1 Image displaying the loss of fingerprints (adermatoglyphia) after chemotherapy in (**a**) case 01, (**b**) case 02, (**c**) case 03, and (**d**) case 04.

Case 03

A 49-year-old woman presented with complaints of bleeding per rectum, diarrhea, and vomiting in December 2022. The diagnostic workup was conclusive of metastatic adenocarcinoma of the rectum (with nonregional lymph nodes). She was planned to undergo palliative chemotherapy and was started on mFOLFOX-4 regimen (modified 5-fluorourocil, oxaliplatin, and leucovorin). She completed six cycles of scheduled chemotherapy. Following this, her PMJAY card was rendered nonfunctional because of her inability to perform biometric registration (►**Fig. 1c**). After 3 months, her disease progressed.

Case 04

A 55-year-old postmenopausal woman was diagnosed with invasive ductal carcinoma of the right breast (cT3N1M0 and ER/PR/Her2negative). She was started on neoadjuvant chemotherapy with four cycles of epirubicin and cyclophosphamide (AC), followed by four cycles of paclitaxel. She underwent modified radical mastectomy. The post-op histopathology was suggestive of residual disease (ypT2N0M0). She received adjuvant radiotherapy and was kept on capecitabine. After completing 3 months of capecitabine, her PMJAY card registration failed because of nonrecognizable fingerprints (►**Fig. 1d**). The recommended duration of her treatment was 6 months to 1 year; nonetheless, she could receive treatment for only 3 months, which increase the risk of recurrence in her case.

Discussion

In the preceding month, 300 chemotherapy procedures (including new cases and follow-up cases) were performed. Of these, 70 were newly diagnosed patients, and 30 of the newly diagnosed patients received 5-FU/Capecitabine based therapy. In this study, the cases of four patients have been presented, detailing their complaints and histories to demonstrate how an uncommon side effect of chemotherapy rendered them ineligible for receiving insurance benefits. To avail of the PMJAY scheme, patients must register using a biometric registration system, which uses fingerprints for identification. However, adermatoglyphia, caused by capecitabine, 5-fluorouracil, and cyclophosphamide, led to treatment interruption as it precluded fingerprint verification. These conditions have been reported in the past. Al-Ahwal reported a case from Saudi Arabia that is comparable to this one, where the patient had endured administrative delays due to the loss of their fingerprints.[5] Azadeh et al also reported cases of patients with cancer undergoing chemotherapy who experienced similar administrative delays in Tehran.[6] Children who are younger than 5 years suffering from curable cancers also become ineligible for the PMJAY scheme due to incompletely developed fingerprints. A report by van Doorn et al involving of 112 patients showed that 70 and 46% patients receiving capecitabine or TKI (tyrosine kinase inhibitors) developed hand-foot syndrome (HFS) or hand-foot skin reaction (HFSR), respectively, but only 14 and 2% treated with capecitabine or TKI had a severe quality loss of fingerprints.[7] The mechanism of HFS causing loss of fingerprints is not well established, but the above reports show that loss of fingerprints may not be seen in all patients receiving capecitabine or TKI irrespective of the grade of HFS and should be considered as a secondary reaction independent of HFS or HFSR.[8]

Table 1 Various techniques used for biometrics verification

Sl. no.	Technique
1	Face recognition
2	Iris recognition
3	Hand geometry
4	Voice recognition
5	Keystroke dynamics
6	Gait
7	Radiofrequency identification technology

Available modalities for biometric evaluation include fingerprint recognition, which is the most commonly utilized method. Other recognition techniques[9,10] are listed in ►**Table 1**. One of the aforementioned alternatives in addition to fingerprint verification has been recommended to be added to the PMJAY software. These alternatives will ensure that those in need continue to benefit from the program. The PMJAY scheme is a game changer in the Indian health care system and a substantial proportion of the Indian population has benefited from this scheme. Patients face multiple problems to obtain this card. After this, if they stop getting benefits of this scheme because of chemotherapy-related toxicities or complications, it understandably becomes bothersome for patients and their families. The deprivation from treatment not only increases their chance of disease recurrence but also increases the demand for palliative and end-of-lifecare services, which are sparsely available in India.[11]

The strength of using a fingerprint scanner is that it is a liable and cheap source of unique identification and is easy to use, whereas other modalities are costly and require training of the staff for appropriate use. Looking at the growing Indian population, implementation of such technologies seems challenging and may add to health care costs. Nevertheless, successful implementation of DigiYatra in airports for quick verification using face recognition of passengers exemplifies a suitable future alternative in health care. Thus, patients in need will never be deprived of the benefits from the PMJAY scheme.

Conclusion

The PMJAY scheme is addressing a relevant need in the Indian health care system. However, some intrinsic procedural issues tend to exclude some patients from getting its benefit. The aforementioned problem statement is a real-world problem. Furthermore, facial recognition and iris scanner seem to be suitable alternatives to fingerprint verification. Adding these identification alternatives for the PMJAY scheme will ensure continuation of benefit from the program.

Authors' Contributions
The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

Patient Consent
Patient consent was taken before the preparation of the manuscript.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
The authors would also like to thank Mr. Mahesh Sharma, in charge of PMJAY at Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, for helping us with details of the PMJAY identification systems required for diagnosis of this unique problem. The authors would also like to thank the TYAcan Foundation for providing financial support to this patient.

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