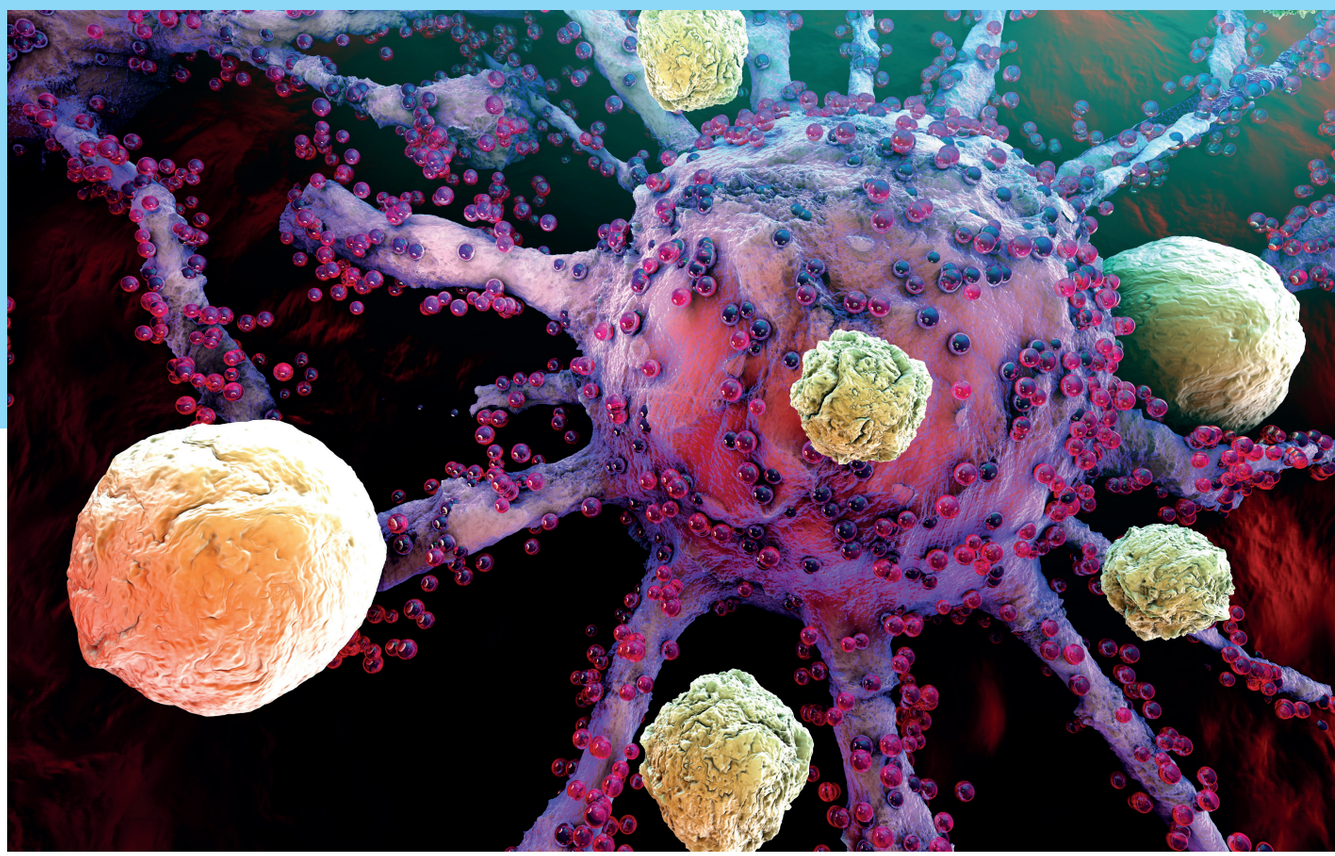
ISSN 0971-5851
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

Number 5 • Volume 45 • Pages 365–460 • October 2024



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Volume 45 • Number 5 • Pages 365–460 • October 2024

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ISSN 0971-5851
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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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Indian Journal of Medical and Paediatric Oncology is indexed in *Emerging Sources Citation Index* and SCOPUS. Thieme Medical Publishers is a member of the CrossRef initiative.

Editorial comments should be sent to journals@thieme.com. The content of this journal is available online at www.thieme-connect.com/products. Visit our Web site at www.thieme.com and the direct link to this journal at www.thieme.com/ijmpo.

Typesetting: Thomson Digital, Noida, India
Printing and Binding: Replika Press Pvt. Ltd.
Printed in India

UPDATE IN ONCOLOGY X

1ST ANNOUNCEMENT

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THEME: CANCER.GENOMICS.PRECISION

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Volume 45, Number 5/2024

Indian Journal of Medical and Paediatric Oncology

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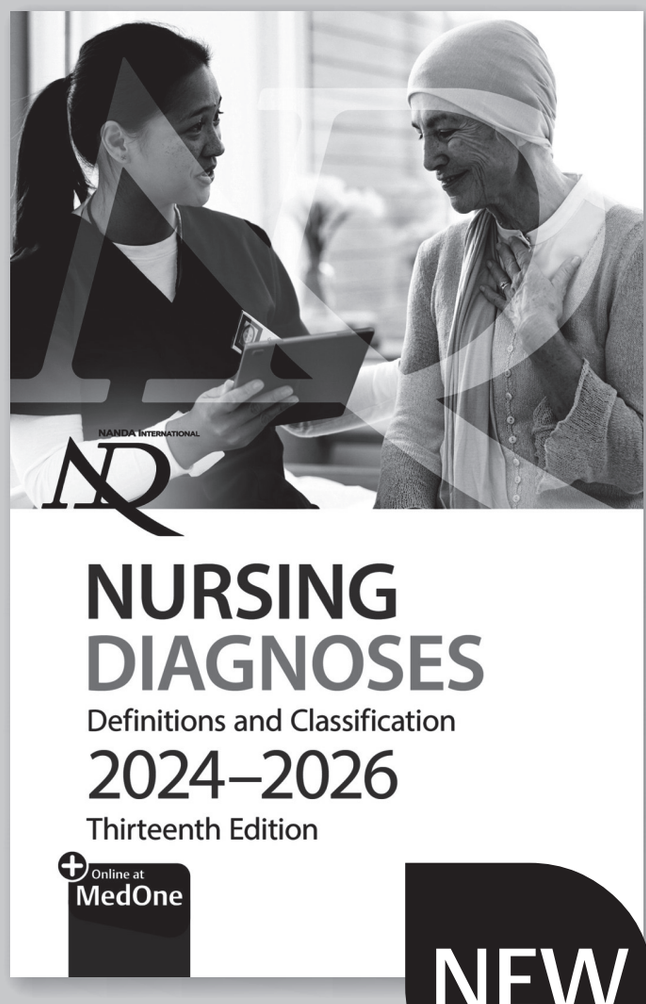

Definitions & Classification

The editors have provided an in-depth discussion of diagnosis and its relationship to assessment. They use Kamitsuru's Tripartite Model of Nursing Practice to distinguish between interdependent interventions based on medical and organizational standards of care and autonomous nursing interventions based on nursing standards of care.

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Management of Locally Advanced Unresectable or Metastatic Urothelial Carcinoma: Expert Opinion from an Indian Panel via Delphi Consensus Method

Senthil Rajappa[1] T. Raja[2] Chirag Desai[3] Amit Joshi[4] Palanki Satya Dattatreya[5] Mohit Agarwal[6] Rahul Sud[7] Anita Ramesh[8] A. K. Vaid[9] Vineet Talwar[10] Amit Rauthan[11] Ashish Kaushal[12] Prabrajya Mohapatra[13] Akhil Kapoor[14]

[1] Department of Medical Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, Telangana, India
[2] Department of Medical Oncology, Apollo Specialty Hospital, Chennai, Tamil Nadu, India
[3] Hemato-Oncology Clinic, Vedanta Institute of Medical Sciences, Ahmedabad, Gujarat, India
[4] Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[5] Department of Medical Oncology, Renova Soumya Hospital, Hyderabad, Telangana, India
[6] Department of Medical Oncology, Fortis Hospital, New Delhi, India
[7] Department of Medical Oncology, Command Hospital Airforce, Bangalore, Karnataka, India
[8] Department of Medical Oncology, Saveetha Medical College and Hospital, Chennai, Tamil Nadu, India
[9] Department of Medical Oncology and Haematology, Medanta Cancer Institute, Medanta – The Medicity, Gurgaon, Haryana, India
[10] Department of Medical Oncology, Rajiv Gandhi Cancer Institute, Delhi, India
[11] Department of Medical Oncology, Hemato-Oncology and Transplant, Manipal Hospital, Bangalore, Karnataka, India
[12] Aagam Clinic, KD Hospital, Ahmedabad, Gujarat, India
[13] Department of Medical Oncology, Apollo Gleneagles Hospital, Kolkata, West Bengal, India
[14] Department of Medical Oncology, Tata Memorial Hospital (TMH) (Homi Bhabha Cancer Hospital [HBCH] and Mahamana Pandit Madan Mohan Malaviya Cancer Centre [MPMMCC]), Varanasi, Uttar Pradesh, India

Address for correspondence Senthil J. Rajappa, DM, Department of Medical Oncology, Basavatarakam Indo American Cancer Hospital and RI, Banjara Hills, Hyderabad 500034, Telangana, India (e-mail: senthiljrajappa@gmail.com).

Ind J Med Paediatr Oncol 2024;45:365–375.

Abstract

Introduction Currently, there are no guidelines for the management of locally advanced unresectable or metastatic urothelial carcinoma (mUC) from an Indian perspective. There is a lack of consensus on the utility of treatment options in first-line (1L) and second-line (2L) settings, especially in cisplatin- and platinum-unfit mUC patient subgroups.

Objective This articles aims to develop evidence-based practical consensus recommendations for the management of mUC in Indian settings.

Methods Modified Delphi consensus methodology was considered to arrive at a consensus. An expert scientific committee of 15 medical oncologists from India constituted the panel. Twelve clinically relevant questions were grouped into five categories for presentation and discussion: (1) cisplatin and platinum ineligibility criteria; (2) programmed death ligand 1 and fibroblast growth factor receptor (FGFR) testing in mUC patients; (3) treatment options in 1L settings; (4) role of switch maintenance; and (5) treatment options in 2L. Statements that reached high ($\geq$ 80%) and moderate (60–79%) levels of consensus in the first round (electronic survey) did not undergo the second Delphi round. The questions that received a low level of consensus ($<$ 60%) were discussed during the virtual meeting.

Keywords
- bladder cancer
- metastatic urothelial carcinoma
- locally advanced
- India
- management
- consensus
- Delphi

article published online
February 10, 2023

DOI https://doi.org/10.1055/s-0042-1760317.
ISSN 0971-5851.

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

Results Renal impairment (creatinine clearance [CrCl] < 60 mL/min) and New York Heart Association class 3 heart failure are important assessment criteria for determining cisplatin ineligibility. Patients are unfit for any platinum-based chemotherapy in case of Eastern Cooperative Oncology Group performance status> 3 or severe renal impairment (CrCl < 30 mL/min). Gemcitabine and platinum with cisplatin over carboplatin were preferred in 1L settings. In patients unfit for cisplatin-based regimens, carboplatin–gemcitabine chemotherapy was preferred over immunotherapy (atezolizumab or pembrolizumab). Selected patients who are platinum ineligible may be considered for immunotherapy. Post-induction chemotherapy, those who do not progress may be strongly considered for avelumab maintenance. Experts recommended erdafitinib in FGFR-positive mUC patients in 2L settings. In FGFR-negative patients, immunotherapy (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine). Enfortumab vedotin and sacituzumab govitecan may be considered for further lines of therapy.

Conclusion Expert panel consensus will offer expert guidance to oncologists/clinicians on the management of mUC in Indian settings.

Key Points

- In 1L settings, the experts preferred gemcitabine and platinum with cisplatin over carboplatin in mUC patients.
- In patients unfit for cisplatin-based regimens, carboplatin–gemcitabine chemotherapy was preferred over immunotherapy (atezolizumab or pembrolizumab). Selected patients who are platinum ineligible (cisplatin and carboplatin) may be considered for immunotherapy (atezolizumab or pembrolizumab) in 1L. Post-induction chemotherapy, those who do not progress should be strongly considered for avelumab switch maintenance.
- Erdafitinib was recommended in FGFR-positive mUC patients in 2L.
- In FGFR-negative patients, platinum-based chemotherapy was suggested in 2L for those relapsing late, immunotherapy (pembrolizumab, nivolumab, or avelumab) for those who did not receive targeted immunotherapy in 1L, and single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) for other mUC patients.

Introduction

Carcinoma of the urinary bladder is a common urological malignancy that causes substantial morbidity and mortality. As per the Global Cancer Observatory: CANCER TODAY (GLOBOCAN) statistics, bladder cancer (BC) ranked 10th in incidence, with approximately 573,000 new cases and 213,000 deaths in 2020.[1] Urothelial carcinoma (UC) is the predominant histologic type of BC and accounts for nearly 90% of all BC cases globally.[2] BC has a wide spectrum of disease severity from low-grade non–muscle-invasive BC (NMIBC) to muscle-invasive disease stage and metastatic lesions associated with poor outcomes.[3] The majority of muscle-invasive tumors are high-grade UCs. A high probability of local/systemic recurrences of muscle-invasive tumors within 36 months after local treatment of primary tumor has been observed.[4] BC diagnosed at earlier stages carry a greater chance of 5-year relative survival compared to later disease stages (►**Table 1**).[5] Overall, 5-year relative survival rate for patients diagnosed with distant metastatic UC (mUC) is roughly 6%.[5] In India, BC is ranked 17th in incidence and 19th in mortality, with significant heterogeneity in incidence rates across different regions of India.[6] The overall incidence rate of BC in India as per the National Cancer Registry Programme report is 2.25 per 100,000 annually (males: 3.67 and females: 0.83).[7] In India, BC patients are more often diagnosed with locally advanced diseases, resulting in poor outcomes. A study by Prakash et al assessed the stage distribution of patients presenting with BC ($N = 419$) to a tertiary care cancer center in Mumbai.[8] The median age of patients at diagnosis was 59 (18–88) years.[8] Around 47% of patients had NMIBC, 36% had muscle-invasive and locally advanced disease, and 17% had metastatic disease.[8] The most common sites of distant metastasis were

Table 1 Five-year relative survival rates of bladder cancer

Stage at diagnosis	5-year relative survival (%)
Stage 0: Noninvasive papillary carcinoma and carcinoma in situ	96
Stage 0–I: Localized (confined to primary sites)	70
Stage III–IV: Regional (spread to regional lymph nodes)	38
Stage IV: Distant (metastasis to lungs, liver, or bones)	6

Abbreviation: SEER: Surveillance, Epidemiology, and End Results.
Note: Adapted from: National Cancer Institute. SEER Cancer Stat Facts for bladder cancer.[5]

bone, lung, liver, pelvic peritoneum, adrenal glands, and nonregional lymph nodes.[8]

The National Comprehensive Cancer Network (NCCN) guidelines recommend either gemcitabine–cisplatin combination chemotherapy or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with growth factor support for cisplatin-eligible mUC patients in first-line (1L) settings.[3] Subsequent switch maintenance may be considered in patients with a nonprogressive disease on 1L platinum-based chemotherapy.[3] However, a substantial proportion of mUC patients are unfit to receive cisplatin-based chemotherapy in 1L settings due to advanced age, poor performance status, impaired renal function, and presence of multiple comorbidities. Currently, there are no defined criteria to establish cisplatin and platinum ineligibility in India, and it varies among different physicians and institutes. In addition, there is a lack of consensus on the utility of different treatment options in cisplatin- and platinum-unfit patients in 1L settings and treatment options in second-line (2L) settings. In this article, we have attempted to summarize expert opinions and recommendations on (1) cisplatin and platinum ineligibility criteria, (2) programmed death ligand 1 (PD-L1) and fibroblast growth factor receptor (FGFR) testing, (3) treatment options in 1L settings, (4) role of switch maintenance after 1L platinum-containing chemotherapy, and (5) treatment options in 2L settings based on the available efficacy and safety data.

Methodology

Panel Selection

A panel of 15 medical oncologists with significant experience in managing BC patients participated in the development of the consensus article.

Evidence Review

A literature review was carried out based on data from the PubMed database to identify relevant articles between January 2001 and March 2022 using keywords such as "urothelial carcinoma," "bladder cancer," "first-line," "second-line," "maintenance," "guidelines," and "management." Twelve clinically relevant questions (►**Supplementary Material**) belonging to five major domains were drafted.

- Cisplatin/platinum ineligibility criteria.
- PD-L1 and FGFR testing.
- Treatment pattern in 1L settings.
- Role of switch maintenance.
- Treatment pattern in 2L settings and subsequent therapy.

An electronic survey link to these questions was sent to all the participants to record their views. Key articles were shortlisted and circulated among the participants before the survey. The "Oxford Centre for Evidence-Based Medicine: Levels of Evidence (LOE)" was used to define the grade or LOE of each recommendation (►**Table 2A**).[9]

Consensus Process

Modified Delphi consensus methodology was considered to arrive at a consensus.[10] ►**Table 2(B)** lists the grades of recommendation (GOR) used during the electronic voting.[11] The level of consensus (LOC) was considered "high" when $\geq$ 80% of participants agreed/strongly agreed or disagreed/strongly disagreed with a particular statement (►**Table 2C**).[12] A "moderate" LOC was achieved when 60 to 79% of participants agreed/strongly agreed or disagreed/strongly disagreed with a particular statement.[12] All the statements that reached a "moderate" and "high" LOC in the first round did not undergo the second Delphi round. The questions that received a "low" LOC ($<$ 60%) were discussed during the Delphi round 2 meeting conducted virtually on April 8, 2022. The final draft of the consensus was e-mailed to the panel for the final review.

Results

The experts ($N = 15$) analyzed evidence, including randomized clinical trials (RCTs), systematic literature reviews, and meta-analyses through a systematic search of MEDLINE (via PubMed), Cochrane Library, and guidelines (NCCN) on mUC management published between January 2001 and March 2022. Experts made their decisions based on the available evidence and current practices in India (during Delphi rounds 1 and 2).

Cisplatin Ineligibility Criteria in Locally Advanced Unresectable UC or mUC

Assessment of performance status and renal function is of utmost importance for treatment selection. The Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$ 2 criterion can strongly predict poor outcomes (increased toxicity and decreased efficacy) in mUC patients treated with cisplatin-based regimens (LOE: 1a).[13] The presence of renal impairment (creatinine clearance [CrCl] $<$ 60 mL/min) is an important exclusion criterion in clinical trials that explore cisplatin-based regimens (LOE: 1a).[13] In addition, the presence of comorbidities such as peripheral neuropathy[13,14] and hearing loss[13,15] are important criteria for determining cisplatin ineligibility (LOE: 2c). Hydration used as part of cisplatin administration can precipitate heart failure in patients with preexisting New York Heart Association (NYHA) class 3 heart failure and hence should be avoided in this subset of patients (LOE: 2c).[13,16]

Consensus/recommendations: Initial clinical evaluation should involve an assessment of medical history, hydration status, urinary obstruction, infection, and metabolic derangement. It is important that these factors are identified early and treated appropriately before deciding on eligibility for cisplatin-based chemotherapy. Experts agreed that renal impairment (CrCl $<$ 60 mL/min) and NYHA class 3 heart failure are important assessment criteria for determining cisplatin ineligibility (GOR: ++; LOC: "high"). Hearing loss of grade $\geq$ 2 should be included in the cisplatin-ineligibility criteria and an attempt should be made to perform audiometry before cisplatin administration (GOR: +; LOC: "high"). In addition, they would consider ECOG PS $\geq$ 2 and grade $\geq$ 2 peripheral neuropathy for determining cisplatin ineligibility in their daily clinical practice (GOR: ++; LOC: "moderate").

Table 2 Definitions: (A) Oxford LOE grading system, (B) grades of recommendation, and (C) level of consensus

(A) Oxford Centre for Evidence-Based Medicine: Level of evidence (LOE)		
LOE	**Therapy/prevention, etiology/harm**	**Prognosis**
1a	Systematic review (with homogeneity) of RCTs	A systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual RCT (with narrow CI)	Individual inception cohort study with > 80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or no case series
2a	Systematic review (with homogeneity) of cohort studies	A systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
2b	Individual cohort study (including low-quality RCTs, < 80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" research and ecological studies	"Outcomes" research
3a	Systematic review (with homogeneity) of case–control studies	
3b	Individual case–control study	
4	Case series (and poor-quality cohort and case–control studies)	Case series (and poor-quality prognostic cohort studies)
5	Expert opinion without an explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without an explicit critical appraisal, or based on physiology, bench research, or "first principles"
(B) Grade of recommendation (GOR)		
++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed	
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed	
+/−	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge, a general recommendation cannot be given	
−	This investigation or therapeutic intervention can be of disadvantage to patients and might not be performed	
−−	This investigation or therapeutic intervention is of clear disadvantage to patients and should be avoided or omitted in any case	
(C) Level of consensus (LOC)		
High	When ≥ 80% of participants agree/strongly agree or disagree/strongly disagree with a statement	
Moderate	When 60–79% of participants agree/strongly agree or disagree/strongly disagree with a statement	
Low	When < 60% of participants agree/strongly agree or disagree/strongly disagree with a statement	

Abbreviations: CI, confidence interval; RCTs, randomized controlled trials.
Adapted from: Oxford Centre for Evidence-Based Medicine: Levels of Evidence,[9] Scharl et al, 2013,[11] and Jünger et al, 2012.[12]

Platinum Ineligibility Criteria in Locally Advanced Unresectable UC or mUC

Patients with ECOG PS > 3, CrCl < 30 mL/min, peripheral neuropathy > 3, NYHA heart failure class > 3, and a combination of ECOG PS 2 and CrCl < 30 mL/min are poor candidates for platinum-based chemotherapy (LOE: 2c).[17] Severe hearing impairment is an exclusion criterion in trials that study platinum-based regimens (LOE: 2c).[18]

Consensus/recommendations: Experts agreed that patients are unfit for any platinum-based chemotherapy in case of ECOG PS > 3 or severe renal impairment (CrCl < 30 mL/min) (GOR: ++; LOC: "high"). Assessment of grade ≥ 2 hearing loss through audiometric evaluation can be performed in patients with mUC and should be included in the platinum-ineligibility criteria (GOR: +; LOC: "high"). In addition, grade > 3 peripheral neuropathy, NYHA class > 3 heart failure, or the combination of ECOG PS 2 and CrCl < 30 mL/min should be considered for determining platinum ineligibility (GOR: ++; LOC: "moderate").

PD-L1 Testing in Locally Advanced Unresectable UC or mUC

The NCCN guidelines recommend early molecular/genomic testing to facilitate treatment decision-making in patients with locally advanced unresectable UC or mUC.[3] A systematic review by Rouanne et al highlighted the use of PD-L1 testing with use of atezolizumab (IMvigor130 [*N* = 851; SP142 assay], IMvigor210 [*N* = 119 cisplatin ineligible; SP142]), and pembrolizumab (KEYNOTE 052 [*N* = 370 cisplatin ineligible; 22C3]) in 1L settings (LOC: 1a).[19] Currently, the use of PD-L1 testing before 1L therapy is advised in mUC patients who are cisplatin ineligible and have no contraindications to the use of immunotherapy. Immune checkpoint inhibitors (ICIs) used in the 1L include atezolizumab and pembrolizumab.[3] However, in platinum-ineligible patients, checkpoint inhibitor (CPI) can be administered irrespective of PD-L1 status.[3] The NCCN guidelines do not recommend PD-L1 testing before the maintenance phase. This is based on the JAVELIN 100 phase 3 trial that was not powered to assess progression-free survival/overall survival (PFS/OS) in the PD-L1-negative mUC patients in maintenance settings (LOE: 2b).[3,20,21] In the 2L setting, PD-L1 testing is not required when assessing eligibility for treatment with ICIs (LOE: 1a).[3,19,22]

Consensus/recommendations: Experts agreed that PD-L1 testing before 1L systemic therapy can be performed in mUC patients who are ineligible to receive cisplatin chemotherapy (GOR: +; LOC: "high"). In platinum-ineligible patients, CPI can be administered irrespective of PD-L1 status (GOR: +; LOC: "high"). PD-L1 testing is not required when assessing eligibility for treatment in maintenance and 2L settings (GOR: +/–; LOC: "high").

FGFR Testing in Locally Advanced Unresectable UC or mUC

Studies have shown that FGFR3 mutation or FGFR2/3 fusion plays a significant role in the development of mUC.[23–25] Currently, FGFR testing (FGFR3 mutation or FGFR2/3 fusion) is recommended after progression on platinum-based chemotherapy by the NCCN group to plan for optimal treatment (FGFR inhibitor or PD-L1 inhibitor [for FGFR-negative patients]) based on the eligibility criteria (LOE: 1a).[3,23–25]

Consensus/recommendations: FGFR mutation testing has not shown benefit for mUC patients in 1L settings. Experts strongly opined that it is important to screen mUC patients for FGFR3 alterations or FGFR2/3 fusion before 2L systemic therapy to plan for optimal treatment (FGFR inhibitor or PD-L1 inhibitor) (GOR: ++; LOC: "high").

►**Table 3** lists recommendations on cisplatin/platinum ineligibility criteria and biomarker testing for management of locally advanced unresectable or mUC.

Treatment Pattern in 1L Settings

Patients eligible for cisplatin-based chemotherapy: The NCCN guidelines recommend either gemcitabine–cisplatin chemotherapy or ddMVAC with growth factor support for cisplatin-eligible mUC patients in 1L settings.[3]

Patients ineligible to receive cisplatin-based chemotherapy: Carboplatin–gemcitabine combination chemotherapy is recommended in cisplatin-ineligible mUC patients in 1L based on the results of phase 1/2 randomized EORTC 30986 trial (overall response rate [ORR]: 41.2%; median OS: 9.3 months) (LOE: 2b).[26] Treatment with an ICI (atezolizumab [PD-L1 inhibitor] or pembrolizumab [PD-1 inhibitor]) could be an alternative option.[3] Currently, the use of PD-L1 testing before 1L therapy is advised in mUC patients who are cisplatin ineligible and have no contraindications to the use of immunotherapy.[3] In phase 2, IMvigor210 cohort study, atezolizumab conferred significant clinical benefits in untreated cisplatin-ineligible mUC.[27] Scoring criteria designated tumors based on tumor-infiltrating immune cells (ICs): (1) IC0 (PD-L1 expression on < 1% of IC), (2) IC1 (PD-L1 expression on ≥ 1% and < 5% of IC), or (3) IC2/3 (PD-L1 expression on ≥ 5% of IC). The study demonstrated favorable durable response rates, survival, and tolerability of atezolizumab in mUC patients in 1L settings.[27] The median OS was 12.3 months in IC2/3 and 19.1 months in IC0/1 group (LOE: 2b).[27] However, in May 2018, the Food and Drug Administration (FDA) issued a safety alert for use of atezolizumab monotherapy in 1L settings due to decreased survival compared to platinum-based chemotherapy in mUC patients who have not received prior therapy and who have low PD-L1 expression.[28] The FDA has restricted the use of atezolizumab in cisplatin-unfit mUC patients with positive PD-L1 status (PD-L1 expression on ≥ 5% of IC) and mUC patients eligible for any platinum-containing chemotherapy regardless of PD-L1 expression in 1L settings.[28] On April 2021, the FDA agreed to continue the accelerated approval of atezolizumab in the frontline treatment of cisplatin-unfit mUC.[29] The efficacy and safety of pembrolizumab were assessed in the phase 2 KEYNOTE-052 trial in 1L settings.[30,31] The study demonstrated the efficacy of pembrolizumab with acceptable tolerability in cisplatin-unfit patients, most of whom were elderly, had poor performance status, or had serious comorbidities. In patients with positive PD-L1 status defined as a combined positive score (CPS) ≥ 10, the median OS was 18.5 months (95% confidence interval [CI]:12.2–28.5 months) (LOE: 2b).[30,31] Frail patients and patients with three or more comorbidities are candidates for best supportive care (BSC) alone instead of systemic therapy in 1L (LOE: 2c).[32–34]

Patients ineligible to receive any platinum-based chemotherapy (cisplatin and carboplatin): On August 2021, the FDA converted the accelerated approval of 1L pembrolizumab in

Table 3 Cisplatin-/platinum-ineligibility criteria and biomarker testing in mUC patients

(A) Cisplatin/platinum ineligibility criteria: Summary of expert recommendations
Expert recommendations on cisplatin-ineligibility criteria
• ECOG PS $\geq$ 2 (LOE: 1a; GOR: ++; LOC: 66.7%).
• CrCl $<$ 60 mL/min (LOE: 1a; GOR: ++; LOC: 86.7%)
• Grade $\geq$ 2 peripheral neuropathy (LOE: 2c; GOR: ++; LOC: 60%)
• NYHA class 3 heart failure (LOE: 2c; GOR: ++; LOC: 80%)
• Grade $\geq$ 2 hearing loss (LOE: 2c; GOR: +; LOC: 80%)
Expert recommendations on platinum (cisplatin and carboplatin)-ineligibility criteria
• ECOG PS $>$ 3 (LOE: 2c; GOR: ++; LOC: 80%)
• CrCl $<$ 30 mL/min (LOE: 2c; GOR: ++; LOC: 80%)
• Grade $>$ 3 peripheral neuropathy (LOE: 2c; GOR: ++; LOC: 60%)
• NYHA class $>$ 3 heart failure (LOE: 2c; GOR: ++; LOC: 60%)
• ECOG PS 2 and CrCl $<$ 30 mL/min are important criteria for determining platinum ineligibility in patients with mUC (LOE: 2c; GOR: ++; LOC: 66.7%)
• Grade $\geq$ 2 hearing loss (LOE: 2c; GOR: +; LOC: 80%)
(B) Biomarker testing in mUC: Summary of expert recommendations
PD-L1 testing before 1L systemic therapy can be performed in mUC patients who are ineligible to receive cisplatin chemotherapy. PD-L1 testing before 1L systemic therapy is not required for those who are ineligible to receive any platinum-based chemotherapy (LOE: 1a; GOR: +; LOC: 80%)
PD-L1 testing is not required when assessing eligibility for ICI maintenance in patients who have not progressed with platinum-containing chemotherapy (LOE: 2b; GOR: +/−; LOC: 80%)
PD-L1 testing is not required when assessing eligibility for treatment in 2L settings. According to current knowledge, a general recommendation cannot be given (LOE: 1a; GOR: +/−; LOC: 80%)
FGFR mutation testing has not shown benefit for mUC patients in 1L settings. A general recommendation regarding FGFR testing before 1L systemic therapy cannot be given (LOE: 2b; GOR: +/−; LOC: 80%)
It is important to screen mUC patients for FGFR alterations before 2L systemic therapy to plan for optimal treatment (LOE: 1a; GOR: ++; LOC: 80%)

Abbreviations: 1L, first-line; 2L, second-line; CrCl, creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; NYHA, New York Heart Association; PD-L1, programmed death-ligand 1.

locally advanced or mUC (cisplatin-unfit patients with PD-L1 CPS $\geq$ 10 or patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status) to a full approval and revised the indication to only cover the treatment of patients who are not eligible for any platinum-containing chemotherapy.[35] Based on the FDA approvals and evidence, the recent 2022 NCCN guideline has recommended: (1) atezolizumab (for patients not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression); or (2) pembrolizumab (for patients who are not eligible for any platinum-containing chemotherapy) (LOE: 2b).[3,27,28,30,31,35]

Consensus/recommendations: Experts agreed that they would prefer carboplatin–gemcitabine chemotherapy followed by avelumab maintenance over ICI monotherapy (atezolizumab or pembrolizumab) in mUC patients with positive PD-L1 status unfit for cisplatin-based regimens in 1L settings (GOR: ++; LOC: "high"). Experts preferred ICI monotherapy (atezolizumab or pembrolizumab) over BSC in patients ineligible for any platinum-based chemotherapy (GOR: ++; LOC: "high"). BSC should be strongly preferred over ICI therapy in patients with: (1) poor performance status, (2) multiple uncontrolled comorbidities, and/or (3) poor access to therapies (GOR: ++; LOC: "high").

Role of ICI–chemotherapy combination therapy: Two trials investigated the relevance of ICI (atezolizumab or pembrolizumab) plus platinum-based chemotherapy combination in 1L settings. The first trial to report was IMvigor130, where atezolizumab plus platinum-based chemotherapy provided PFS benefit (8.2 vs. 6.3 months; $p = 0.007$); however, OS was not significant after a median follow-up of 11.8 months compared to placebo plus platinum-based chemotherapy.[36] The KEYNOTE 361 study had a similar design and investigated pembrolizumab plus platinum–gemcitabine versus chemotherapy plus placebo in 1L settings.[37] The study revealed no benefit of this combination in terms of PFS or OS.[37]

Consensus/recommendations: Experts agreed that immunotherapy (atezolizumab or pembrolizumab) plus platinum–gemcitabine chemotherapy is not suitable in mUC patients in 1L settings (GOR: −; LOC: "high").

Role of Switch Maintenance in Locally Advanced Unresectable UC or mUC After Platinum-Based Chemotherapy

The JAVELIN Bladder 100 phase 3 RCT explored the impact of switch maintenance with PD-L1 inhibitor avelumab plus BSC versus BSC alone in mUC not progressed with 1L platinum-containing chemotherapy (complete or partial response vs. stable disease).[21] Patients were categorized as having PD-L1-positive status if at least one of the three criteria were met: (1) at least 25% of tumor cells stained for PD-L1, (2) at least 25% of ICs stained for PD-L1 if more than 1% of the tumor area contained ICs, or (3) 100% of ICs stained for PD-L1 if no more than 1% of the tumor area contained ICs.[21] Addition of maintenance avelumab to BSC significantly prolonged median OS (21.4 months; 95% CI: 18.9–26.1) as compared with BSC alone (14.3 months [95% CI: 12.9–17.9]; $p = 0.001$) (LOE: 1b).[21] With extended follow-up ($\geq$ 38 months), median OS remained significantly longer in the avelumab plus BSC (23.8 months [95% CI: 19.9–28.8]) as compared to BSC alone (15.0 months [95% CI: 13.5–18.2]; $p = 0.0036$) in unresectable locally advanced UC or mUC without disease progression.[38] Another phase 2 RCT investigated the impact of switch maintenance with PD-1 inhibitor pembrolizumab in mUC patients achieving at least stable disease on 1L platinum-based chemotherapy. In this study, the OS was not significantly different (22 vs. 18.7 months) in patients randomly assigned to maintenance pembrolizumab versus placebo (LOE: 2b).[39]

Consensus/recommendations: Experts strongly recommended avelumab switch maintenance plus BSC in mUC patients with nonprogressive disease after 4 to 6 cycles of 1L platinum-containing chemotherapy (GOR: ++; LOC: "high"). They would not prefer pembrolizumab switch maintenance due to no significant OS benefit in mUC patients (GOR: −; LOC: "high"). They would consider BSC alone in patients with poor performance status and lack of access to immunotherapies (GOR: +/−; LOC: "high").

Patient profiles suitable for avelumab switch maintenance: Avelumab switch maintenance plus BSC provided an OS and PFS benefit in patients with PD-L1-positive or PD-L1-negative tumors, with a potentially greater benefit in patients with PD-L1-positive tumors.[21] Avelumab maintenance significantly prolonged OS in the PD-L1-positive mUC patients; OS at 1 year was 79.1% in the avelumab group versus 60.4% in the control group (BSC alone; $p < 0.001$) (LOE: 1b).[21] With extended follow-up ($\geq$ 38 months), median OS remained significantly longer in the avelumab plus BSC (30.9 months [95% CI: 24.0–39.8]) as compared to BSC alone (18.5 months [95% CI: 14.1–24.2]; $p = 0.0064$) in unresectable locally advanced UC or mUC patients with PD-L1-positive tumors.[38] The JAVELIN Bladder 100 phase 3 trial was not powered to assess PFS/OS in the PD-L1-negative mUC patients in maintenance settings.[21] In mUC patients with PD-L1-negative tumors, the median OS was 18.8 months (95% CI: 13.3–22.5) in the avelumab plus BSC group versus 13.7 months (95% CI: 10.8–17.8) in the BSC alone (hazard ratio: 0.85; 95% CI: 0.62–1.18) (LOE: 2b).[21] The trial demonstrated OS benefits with avelumab switch maintenance in a range of patient subgroups (categorized by age, ECOG PS 0/1, prior chemotherapy regimen, response to chemotherapy, site of baseline metastasis, CrCl) not progressed with 1L platinum-containing chemotherapy (LOE: 1b).[20,21]

Consensus/recommendations: Experts agreed that avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with ECOG 0/1, age < 65 years, regardless of PD-L1 status, CrCl, site of metastasis, and chemotherapy (gemcitabine with cisplatin or carboplatin). The patient profiles that received moderate consensus during the discussion were: (1) stable disease after 1L platinum-containing chemotherapy, (2) visceral metastasis after 1L platinum-containing chemotherapy, and (3) age $\geq$ 65 years (GOR: ++).

►**Table 4** lists the recommendations for 1L systemic therapy and switch maintenance after 1L platinum-containing chemotherapy.

Treatment Pattern in 2L and Subsequent Therapy

In the phase 3 KEYNOTE-045 RCT, pembrolizumab conferred significant OS benefits in 2L (10.3 vs. 7.4 months; $p = 0.002$) as compared to the chemotherapy group (paclitaxel, docetaxel, or vinflunine) in mUC patients who progressed during or after the receipt of platinum chemotherapy (LOE: 1b).[40] Nivolumab, a fully human immunoglobulin G4 PD-1 ICI, demonstrated clinical benefit (ORR was 19·6% [95% CI: 15.0–24.9]) in a phase 2, single-arm study in mUC patients whose disease progressed or recurred despite previous treatment with at least one platinum-based chemotherapy regimen (LOE: 2b).[41] Recently, the efficacy and safety of avelumab in 2L were assessed in phase 1b JAVELIN Solid Tumor study. Avelumab therapy resulted in a median OS of 7.0 months and a 24-month OS rate of 20.1% (LOE: 2b).[42] For management of mUC patients with FGFR alternations, the NCCN guideline recommends erdafitinib, a tyrosine kinase inhibitor of FGFR1–4, in 2L based on the promising result from the phase 2 BLC2001 study.[43] The confirmed response rate to erdafitinib therapy was 40% and the median OS was 13.8 months. Among patients who had undergone prior immunotherapy, the response rate was 59% (LOE: 2b).[43] The indication of atezolizumab was withdrawn by the FDA in March 2021 in mUC patients previously treated with platinum-based chemotherapy based on the results of the phase 3 IMvigor211 trial.[44] The trial failed to meet its primary endpoint of OS benefit in mUC patients with positive PD-L1 status (IC2/3; 11.1 vs. 10.6 months; $p = 0.41$) as compared to chemotherapy (vinflunine, paclitaxel, or docetaxel).[44,45] The NCCN guidelines recommend: (1) rechallenge with gemcitabine and cisplatin or carboplatin or MVAC in patients who relapse after a year of last platinum exposure, (2) erdafitinib in patients with FGFR3 or FGFR2 genetic alterations, or (3) ICI therapy (pembrolizumab, nivolumab, or avelumab) in patients who have not received ICI in 1L settings.[3]

Consensus/recommendations: Experts recommended erdafitinib in FGFR-positive mUC patients in 2L settings (GOR: ++; LOC: "high"). Experts agreed that in FGFR-negative patients, ICIs (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine).

Table 4 First-line systemic therapy and switch maintenance for locally advanced or mUC

(A) 1L systemic therapy for locally advanced unresectable UC or mUC: Summary of expert recommendations
Treatment of cisplatin-ineligible mUC patients with positive PD-L1 status Carboplatin–gemcitabine chemotherapy is preferred over ICI monotherapy (atezolizumab or pembrolizumab) in mUC patients with positive PD-L1 status deemed unfit for cisplatin-based therapy in 1L settings (LOE: 2b; GOR: ++; LOC: 80%) ***Treatment of mUC patient ineligible for any platinum-based chemotherapy (cisplatin and carboplatin ineligible)*** • ICI monotherapy (atezolizumab or pembrolizumab) can be preferred over BSC in patients ineligible for any platinum-based chemotherapy (LOE: 2b; GOR: ++; LOC: 80%) • BSC is strongly preferred over ICI therapy in patients with: (1) poor performance status; (2) multiple uncontrolled comorbidities; and/or (3) poor access to immunotherapies (LOE: 2c; GOR: ++; LOC: 80%) ***Scope of immunotherapy–chemotherapy combination in 1L treatment settings*** • Immunotherapy (atezolizumab or pembrolizumab) plus platinum–gemcitabine chemotherapy is not suitable in mUC patients in 1L treatment settings (LOE: 1b; GOR: −; LOC: 80%)
(B) Switch maintenance for locally advanced unresectable UC or mUC patients after 1L platinum-containing chemotherapy: Expert recommendations
Switch maintenance in the general population • Avelumab switch maintenance plus BSC is strongly recommended in mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 100%) • Pembrolizumab switch maintenance is not suitable after 1L platinum-containing chemotherapy due to no OS benefit in mUC patients (LOE: 2b; GOR: −; LOC: 80%) • BSC instead of switch maintenance can be considered in patients with poor performance status and lack of access to immunotherapies (LOE: 2c; GOR: +/−; LOC: 80%)
Patient profiles suitable for avelumab switch maintenance therapy ***PD-L1 status*** • Avelumab switch maintenance plus BSC is strongly recommended in PD-L1-positive mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab switch maintenance plus BSC can be performed in PD-L1-negative mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 2b; GOR: ++; LOC: 80%) **Prior chemotherapy regimen** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients not progressed on 1L gemcitabine–carboplatin or gemcitabine–cisplatin-based chemotherapy (LOE: 1b; GOR: ++; LOC: 93.3%) ***Response to chemotherapy*** • Avelumab switch maintenance therapy is beneficial and recommended in mUC patients with partial and complete response after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab maintenance therapy is also recommended in mUC patients with stable disease after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 66.7%) **Type of metastases** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with nonvisceral metastasis after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab switch maintenance therapy is beneficial in mUC patients with visceral metastasis after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 73.3%) **ECOG status** Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with ECOG status 0/1 (LOE: 1b; GOR: ++; LOC: 93.3%) **CrCl** Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients regardless of CrCl (< 60 mL/min and ≥ 60 mL/min) (LOE: 1b; GOR: ++; LOC: 73.3%) **Age** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with age < 65 years (LOE: 1b; GOR: ++; LOC: 100%) • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with age ≥ 65 years (LOE: 1b; GOR: ++; LOC: 66.7%)

Abbreviations: 1L, first-line; BSC, best supportive care; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; PD-L1, programmed death-ligand 1; UV, urothelial carcinoma.

Patient eligibility should be determined before therapy based on the available efficacy and safety data. On the other hand, chemotherapy (paclitaxel, docetaxel, or vinflunine) can be considered in patients who are not eligible for ICI therapy or have poor access to ICI therapy. Experts strongly opined that pembrolizumab can be preferred as it has strong phase 3 clinical evidence with OS benefit (GOR: ++; LOC: "high") as compared to nivolumab (GOR: +; LOC: "high").

Patient profiles suitable for ICI in 2L: Experts agreed that ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable and can be recommended in patients with ECOG status 0/1 (GOR: ++; LOC: "high"). In addition, ICI therapy can be considered in patients with: (1) prior cisplatin chemotherapy, (2) PD-L1 (IC 2/3), and (3) visceral disease (GOR: ++; LOC: "moderate").

Scope of antibody–drug conjugates (ADCs): In phase 3 EV-301 trial, the efficacy of enfortumab vedotin, a nectin-4-directed

ADC, was assessed in patients previously treated with platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.[46] The study demonstrated that median OS was significantly longer in the enfortumab vedotin treatment arm (12.88 months [95% CI: 10.58–15.21) as compared to the chemotherapy group (docetaxel, paclitaxel, or vinflunine) (8.97 months [95% CI: 8.05–10.74]; $p = 0.001$) (LOE: 1b).[46] Another phase 2, open-label (TROPHY-U-01) cohort study investigated the role of TROP-2-directed ADC sacituzumab govitecan in mUC patients who progress on platinum-based combination chemotherapy and ICI therapy.[47] The median OS achieved with sacituzumab govitecan therapy was 10.9 months (95% CI: 9.0–13.8 months) (LOE: 2b).[47]

Consensus/recommendations: Experts agreed that enfortumab vedotin is a suitable treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (GOR: ++; LOC: "moderate"). Currently, enfortumab vedotin is available only on a compassionate basis in India. Sacituzumab govitecan is another treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (GOR: ++; LOC: "low").

OS improvement from the start of 1L therapy: Experts opined that 1L platinum-based chemotherapy (4–6 cycles) followed by avelumab switch maintenance with BSC is most useful in terms of OS improvement from the start of 1L therapy and can be recommended (GOR: ++; LOC: "high").

►**Table 5** lists the recommendations for 2L systemic therapy for the management of mUC.

Discussion

Clinical and Research Implications

Treatment of UC has evolved over the last few years with improved outcomes across different disease stages. ICI and targeted therapies have emerged as new options for the treatment of persistent diseases. In India, there are no country-specific guidelines or recommendations for the management of locally advanced unresectable or mUC. Furthermore, due to the scarcity of RCTs conducted in India and the lack of local guidelines or recommendations, oncologists rely on data from the Western world. Currently, there are no defined criteria to establish cisplatin and platinum ineligibility in India, and it varies among different physicians and institutes. There is a lack of consensus on the utility of treatment options, especially in cisplatin- and platinum-unfit mUC patient subgroups. To the best of our knowledge, this is the first evidence-based practical consensus document to guide clinicians on the management of mUC in Indian settings. This consensus document will offer expert guidance to Indian oncologists and help achieve consistency in mUC management across various healthcare settings.

Strengths: The members of the panel (in the space of genitourinary oncology) were selected to best represent the breadth of knowledge and clinical expertise in the field from all over India. There was no selection bias during the development of the expert committee. All experts actively participated during the consensus process. The responses of all panelists were generated in the form of graphs (GOR vs. response in percentage) to ensure the protection of participants' data.

Table 5 Second-line systemic therapy for locally advanced or mUC

2L systemic therapy for locally advanced unresectable UC or mUC: Expert recommendations
• Erdafitinib is recommended in FGFR-positive mUC patients in 2L settings (LOE: 2b; GOR: ++; LOC: 80%) • In FGFR-negative patients, ICI (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine) in 2L settings. Pembrolizumab has strong phase 3 data in terms of OS and can be preferred (LOE: 1b; GOR: ++; LOC: 80%) over nivolumab (LOE: 2b; GOR: +; LOC: 80%) in 2L settings • Enfortumab vedotin is a suitable treatment option in mUC patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (LOE: 1b; GOR: ++; LOC: "moderate"). Currently, enfortumab vedotin is available only on a compassionate basis in India • Sacituzumab govitecan is another treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (LOE: 2b; GOR: ++; LOC: "low")
Patient profiles suitable for ICI in 2L settings • ECOG PS status: ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable and can be recommended in patients with ECOG status 0/1 in 2L settings (GOR: ++; LOC: 86.7%) • PD-L1 status: ICI therapy (pembrolizumab, nivolumab or avelumab) can be considered in PD-L1 (IC 2/3 [GOR: ++; LOC: 60%] and IC 1 [GOR: +; LOC: 73.3%]) in 2L settings • First-line chemotherapy: ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable in patients with prior cisplatin chemotherapy in 2L settings (GOR: ++; LOC: 73.3%) • Extent of involvement: ICI therapy (pembrolizumab, nivolumab, or avelumab) can be considered in patients with visceral disease in 2L settings (GOR: ++; LOC: 60%)
OS improvement from the start of therapy: Expert recommendations
1L platinum-based chemotherapy (4–6 cycles) followed by avelumab switch maintenance with BSC is most useful in terms of OS improvement from the start of 1L therapy and can be recommended (GOR: ++; LOC: 100%)

Abbreviations: 2L, second-line; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; UV, urothelial carcinoma.

Limitation: The patient's voice was not included in the consensus process.

Conclusion

In this article, we have attempted to summarize the Indian consensus on the management of locally advanced unresectable UC or mUC. Patients with treatment-naive mUC should be classified according to cisplatin and platinum eligibility based on clear definitions. In a 1L setting, the experts preferred gemcitabine and platinum with cisplatin over carboplatin. Selected patients who are platinum ineligible may be considered for atezolizumab or pembrolizumab. Post-induction chemotherapy, those who do not progress should be strongly considered for avelumab maintenance. Experts recommended screening mUC patients for FGFR3 alterations or FGFR2/3 fusion before deciding on 2L therapy. Options for 2L therapy include platinum-based chemotherapy for those relapsing late, targeted therapy with erdafitinib for patients with FGFR alterations, ICI (pembrolizumab, nivolumab, or avelumab) for those who have not received ICI in 1L settings, and single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) for others. Enfortumab vedotin and sacituzumab govitecan should be considered for further lines of therapy.

Authors' Contributions

All authors have contributed equally to the concept, design, editing, review, and finalization of manuscript.

Funding

This study is supported by Pfizer India Ltd.

Conflict of Interest

None declared.

Acknowledgment

We would like to thank BioQuest Solutions Pvt Ltd for their editorial support.

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The Effects of Dietary Nutrient Intake on Cervical Cancer: A Brief Review

Suchismita Nath[1] Sultana S. Nasrin[1] Amrita Samanta[1] Anzum Nuzhad[1] Pritha Ghosh[1] Atanu Manna[1] Satyasundar Pradhan[1] Suresh Maity[1] Srikanta Pal[1] P.K. Das Mohapatra[1] Subhas Chandra Jana[1]

[1] Department of Microbiology, Raiganj University, Raiganj, Uttar Dinajpur, West Bengal, India

Address for correspondence Dr. Subhas Chandra Jana, M.Sc, Ph.D., Head of Department of Microbiology, Raiganj University, Raiganj, West Bengal, India (e-mail: subhasjana1959@gmail.com).

Ind J Med Paediatr Oncol 2024;45:376–382.

Abstract

Cervical cancer (CC) results from a subsequent process, starting from the infection of normal cervical epithelium with oncogenic human papillomavirus and gradually progressing to cervical intraepithelial neoplasia (CIN), before finally developing into invasive cervical cancer (ICC). Over recent decades, dietary micronutrients have gained much attention due to their pivotal role in cancer prevention. We reviewed several relevant literature studies to investigate the protective roles of dietary nutrient intake in CC. Dietary intake of vitamin C, green–yellow vegetables, and provitamin A carotenoids that are rich sources of antioxidants may widely inhibit the process of CC development, whereas vitamins A and D might be more helpful in preventing the early events in the disease development. Vitamin E, lycopene, and folate are more effective for the treatment of high-grade CIN. Fruits exert their protective effects in the late stages of the cancer process, thus playing a vital role in ICC prevention. Polyphenols, flavonoids, and polyunsaturated fatty acids are more often used in cases of CC in combination with chemotherapy and radiotherapy. Thus, as a primary prevention strategy, the health benefits of various nutrients in CC must be clarified by vitro and in vivo approaches rather than epidemiological studies.

Keywords
- diet
- nutrition
- HPV
- cervical dysplasia
- cervical cancer

Introduction

Diet and nutrition not only serve as the source of important physiologically functional components of human beings, but they also play crucial roles in cancer management. Dietary factors approximately contribute to 20 to 60% of all cancers worldwide.[1,2] Cervical cancer (CC) ranks as the third most commonly diagnosed cancer type and fourth leading cause of cancerous deaths in women worldwide.[3,4] The Global Cancer Observatory estimates of the incidence rate of CC due to human papillomavirus (HPV) in 2020 were 604,127 and mortality rates were 341,831 globally (95% UI).[5] Oncogenic HPV is a necessary but insufficient risk factor for the development of cervical carcinoma, as most HPV infections clear spontaneously without leading to any cervical cytological abnormalities.[6] However, the persistence of genital HPV infection that might progress to cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC) is influenced by a variety of infectious, behavioral, lifestyle-associated cofactors.[7,8] Various studies on risk factors have associated the role of the diet with CIN, hypothesizing that women with a relatively high dietary intake of certain nutrients have a reduced risk of developing intraepithelial and invasive cervical lesions. Of particular interest are antioxidants that play major roles in cell survival, proliferation, and differentiation, such as vitamins

article published online
April 24, 2023

DOI https://doi.org/10.1055/s-0043-1768049.
ISSN 0971-5851.

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

A, D, C, and E,[1,2,9–11] tea polyphenols (TPPs),[12] flavonoids,[1,2] tocopherol, and provitamin A carotenoids[10,13–17]; regulators of DNA synthesis and repair such as folate[10,18–20]; and inflammatory response relievers such as polyunsaturated fatty acid (PUFA).[21]

Understanding the effects of diet and nutrition on CC development is very important for the management of public health concerns. For these reasons, it is necessary to understand the roles of various dietary nutrients in CC development. This paper reviews the current issues, effects, and possible protective mechanism of these dietary micronutrients in CC in relation to each stage of CC development.

Role of Dietary and Nutrient Intake on Cervical Cancer

In India and other developing nations, cervical cancer (CC) is the second most common cancer among women of reproductive age.[22] Infection with HPV is the disease's main underlying cause. It usually takes nearly 10 to 20 years for a precancerous lesion to develop into cancer. CC is also proven to be associated with many factors such as the age at marriage, age at the consummation of marriage, parity, history of promiscuity, smoking habits, and the use of oral contraceptives (OC).[23] But the dietary intake of various nutrients plays a vital role in either the development or prevention of CC.

Normal metabolic activities and lifestyle factors such as smoking, exercise, and diet generate reactive oxygen species (ROS). Oxidative stress, induced by the overproduction of ROS, causes oxidative damage to biomolecules such as lipids, proteins, and DNA. Thus oxidative stress has been implicated in the development of several chronic diseases, one of which is cancer. Antioxidant deficiency might render individuals more vulnerable to oxidative stress, thereby increasing the risk of cancer occurrence. Exogenous antioxidant supplementation has been proven to alleviate oxidative damage by scavenging ROS and reducing the oxidation of cellular biomolecules.[24] Thus, dietary patterns have a protective effect against the development of a variety of cancers, particularly those of epithelial origin.[25] So the consumption of more antioxidant-containing food such as vegetables, legumes, fruits, and nuts can significantly reduce the risk of any cancer including CC. Barchitta et al reported that a western diet, which includes red and processed meats, salty foods such as pickles and salted/dried fish, dipping sauces, chips, snacks, instant noodles, and low intake of olive oil, is associated with a higher risk of HPV infection.[26] Additionally, women who showed low adherence to a Mediterranean diet (MD), which includes vegetables, legumes, fruits, nuts, milk, cereals, fish, and a high ratio of PUFA, were posed to a greater risk of HPV infection.[26,27] The author demonstrated a direct relationship between the increased intake of MD and the slowdown of progression of hrHPV infection, thus playing a protective role in the onset of neoplasia. As a result, a 60% reduction in CC risk can be attained with high adherence to MD.[26]

Recently, Yang et al reported that dietary oleic acid commonly found in edible oils exerts a stimulatory effect on cancerous cell growth and metastasis of the cervix.[28] Brock et al and Delam et al reported that a diet low in citrus fruits and green-yellow vegetables (green vegetables, carrots, and pumpkins), which are rich sources of antioxidants can elevate the risk of ICC.[23,29] The roles of dietary and nutrient intake in preventing various stages of CC are discussed below, and ►**Fig. 1** depicts the pictorial representation of the same.

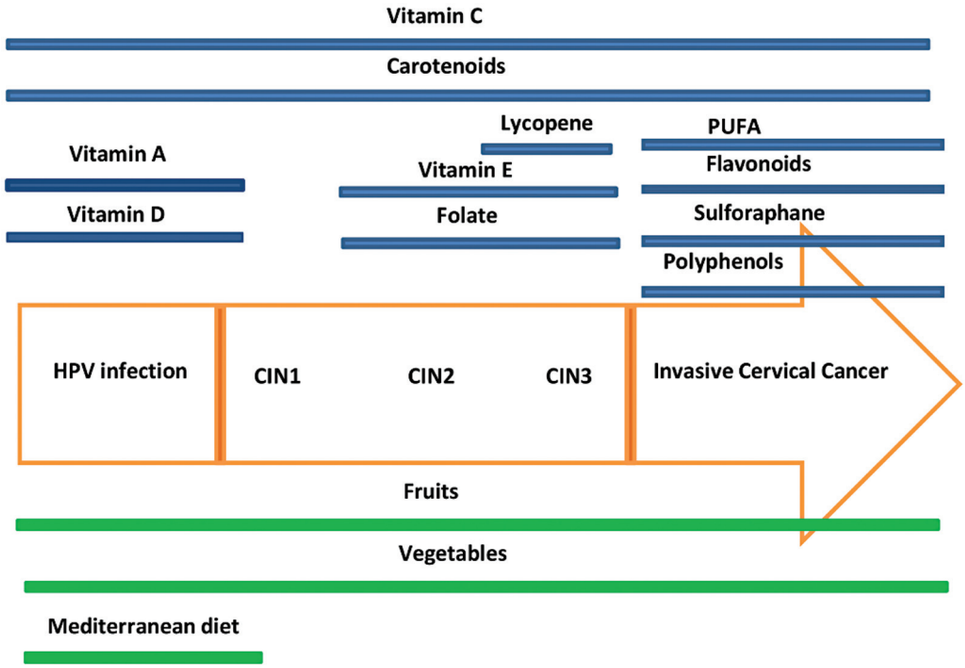

Fig. 1. Role of various nutrients on the development of cervical cancer.

Carotenoids

Carotenoids are pigments that produce the red, orange, and bright yellow colors seen in plants, fruits, and vegetables. There are more than 600 different types of carotenoids. α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene are among the most common dietary carotenoids. Few of them (e.g., alpha-carotene, beta-carotene, and beta-cryptoxanthin) can be converted into vitamin A when released into the body. Beta-carotene, named provitamin A, is transformed into vitamin A by the liver, according to the body's needs. It is the most powerful precursor of vitamin A, followed by alpha-carotene, beta-cryptoxanthin, and other carotenoids. Vitamin A deficiency stimulates oxidative stress, cellular damage, and inhibition of cell repair function.

Studies indicated inverse associations between dietary and serum antioxidant micronutrients like provitamin A carotenoids (precursor of vitamin A) like α-carotene, β-carotene, lutein/ zeaxanthin, and cryptoxanthin and the risk of CC, especially for squamous-cell carcinoma.[10,15–17] However, they did not observe any protective effects of dietary retinol (preformed vitamin A) against CC as it might be associated with early events in the HPV infection process and, therefore, may be more effective in preventing low-grade CIN.[10,15] Blood retinol would not be expected to exert an effect since levels of retinol are under homeostatic control and show little variation except under extreme conditions of over- or undernutrition.[30]

Two population-based case-control studies analyzing the concentration of a variety of serum carotenoids of ICC patients and controls reported that women possessing low serum levels of total carotenoids (alpha-carotene, beta-carotene, and cryptoxanthin) are significantly more prone to ICC as compared to controls,[14,31] whereas the supplementation of oral beta-carotene has been reported to prevent CC.[13]

However, contradictory results were obtained in a Japanese case-control study (Nagata et al) where it was reported that carotene consumption was not significantly associated with protection against cervical dysplasia. A low serum carotenoid concentration found in cases indicated that it was a result of the disease rather than a cause of its occurrence.[10]

Serum concentrations of lycopene carotenoid have also been linked to CC. A low concentration of this micronutrient in serum has the propensity to increase the risk of developing CIN3, whereas medium to high levels were observed to reduce the risk of CIN3 development.[11] In summary, lycopene might be more effective for preventing high-grade CIN rather than primary HPV infection. Lycopene is a bright red pigment and phytochemical from tomatoes, red carrots, watermelons, and red papayas. It exerts antioxidant activity and has chemopreventive effects in different types of cancer. Its anticancer property is imparted by its ability to activate cancer preventive enzymes such as phase II detoxification enzymes. It has been found to inhibit human cancer cell proliferation and to suppress insulin-like growth factor-I-stimulated cell growth.[12]

Therefore, it can be concluded that serum carotenoids provide overall protection against CC development. Its possible mechanism of action is via its antioxidant activity involved in scavenging ROS, thus reducing toxic effects on cell membranes, cellular proteins, and nucleic acids.[29,32]

Vitamins

In recent decades, dietary antioxidants, such as vitamins, have received much attention in relation to cancer prevention.

Fruits (mainly oranges, lemons, strawberries, blackcurrants, and kiwis) and vegetables (mainly tomato, broccoli, and sweet pepper) are rich sources of vitamin C. Vitamin C, also known as ascorbic acid, has several important functions like protecting and maintaining healthy skin, blood vessels, bones, and cartilage while also helping with wound healing.[33] A meta-analysis by Cao et al suggests that there is a significant inverse association between vitamin C intake and the risk of CIN and the association was dose dependent. Notably, increased vitamin C intake by 50 mg/day was significantly correlated with a reduced risk of ICC by 8%.[34] The intake of vitamins C and E may widely inhibit the process of CC development. Slattery et al and Kim et al reported that the intake of vitamins C and E significantly lowered CC risk in nonsmokers as well as in smokers. The reason behind their protective function is that both of these vitamins are known to be antagonists to nitrosamines which are predominant in side-stream smoke than in mainstream smoke, thus efficiently reducing the chances of CC in passive smokers.[9,10] The possible role of vitamin C is the enhancement of cellular immunity, maintenance of the intercellular matrix, and an antioxidative property.[16] Vitamin C is a potent antioxidant that has antineoplastic effects on the cervix. Vitamin C was demonstrated to increase the drug sensitivity of cervical carcinoma cells by stabilizing P53, which was targeted by HPV oncoproteins for degradation and hence causes cell cycle arrest. Antioxidants are able to reduce the toxic effects of ROS, which otherwise lead to changes in the distribution and function of cellular receptors through affecting the fluidity and integrity of the membrane in immunological cells. Free radical is apt to cause extensive damage to DNA, protein, and lipids. Vitamin C could settle this situation by inhibiting DNA adduct formation, thus enhancing mucosal immune response to infection and scavenging the free radicals. Besides, matrix metalloproteases (MMPs), tumor cells secrete enzymes, that digest the membrane and then allow tumor cells to invade adjacent tissues, eventually resulting in migration of cancer cells. Notably, vitamin C can inhibit MMP production and prevent invasion of cancer cells in vitro, suggesting its potential protective effect on CC development.[34]

Vitamin E is a fat-soluble antioxidant that exists in many foods including wheat germ oil, sunflower oil, and safflower oils. It represents a family of compounds comprising both tocopherols and tocotrienols, and in particular, alpha-tocopherol is the most bioactive form of vitamin E that stops the production of ROS when fat undergoes oxidation.[12]

Serum concentrations of vitamin E (α- tocopherol and γ-tocopherol) have been closely associated with CC. A low concentration of this vitamin in serum increases the risk of

developing CIN3, whereas medium to high levels were observed to reduce the risk of CIN3 development.[11] In summary, vitamin E might be more effective for preventing high-grade CIN. Some anti-inflammatory mechanisms have been reported for tocopherols, such as inhibitory protein kinase C (PKC) activity, inhibitory activity of enzymes involved in eicosanoid biosynthesis, and inhibiting cyclooxygenase-2-mediated biosynthesis of PGE2 (prostaglandin E2).[32]

After exposure to ultraviolet-B light, vertebrates can generate vitamin D in their skins. Light-exposed mushrooms are also an excellent source of vitamin D. Vitamin D promotes calcium absorption in the small intestine and maintains adequate serum calcium needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Vitamin D has other roles, including the modulation of cell growth, neuromuscular and immune functions, and the reduction of inflammation. Stefanska et al reported that vitamin D particularly D3 was associated with PTEN induction as well as p21 up-regulation, thus suppressing tumor formation.[12,35] Due to its anti-inflammatory activities, vitamin D may be useful for ameliorating clinical symptoms in patients with HPV infection. Schlte-Uebbing et al also reported that treatment with vitamin D vaginal suppositories (12,500 IU, three nights a week, for 6 weeks) resulted in antidysplastic effects in the CIN 1 group, but that it did not affect the CIN 2 group.[36] Özgü et al showed that the 25-hydroxy vitamin D level in 22 HPV-positive patients was significantly lower than that in 62 HPV-negative patients.[37] These findings may be explained by the assumption that vitamin D deficiency can cause a persistent HPV infection and thus lead to the development of CIN. However, a high intake of vitamin D may therefore suppress persistent HPV infection and prevent the development of CIN 1.[1,2]

Folate

Folate (vitamin B9) plays an important role in red blood cells, DNA synthesis, DNA repair, DNA methylation, and cell proliferation.[38] Many vegetables and pulses are rich sources of folate, with folate concentrations up to 600 pg/100 g in some beans and chickpeas and around 200 pg/100 g in leafy vegetables. A sort of general rule is that the lower the water content in the vegetable, the higher the folate concentration, and therefore leafy vegetables are good folate sources (folium means leaf). Folate concentrations in fruits and berries are usually one-tenth those of vegetables, ranging from a few pg to approximately 50 pg/100 g.[39]

The dietary effect of folic acid on CC has been quite controversial. The intake of folate may prevent or inhibit HPV infection from progressing to various grades of CIN. The studies of Butterworth et al and Kim et al suggested that low plasma folate levels can be associated with an increased risk of cervical dysplasia and dietary supplementation could lead to regression of dysplastic lesions, thus supporting the protective effects of folic acid on CC.[10,18] Similar results were observed by Kwanbunjan et al in a case-control study. The author reported an association between low serum folate levels and high risk of developing both CIN1 and CIN2/3.[19] However, a medium serum folate concentration was associated with a high risk of developing CIN1 but not CIN2/3. Thus, dose-responsive serum folate levels might be useful for the prevention of CIN2/3.[20]

However, Brock et al, Verreault et al, and Palan et al failed to observe a relation between dietary intake of folic acid and the risk of ICC.[16,29,40] A study by Rampersaud et al (2002) mitigated the controversy related to the role of folate on CC, by supporting the latter studies that there is no inverse association between serum folate and the risk of CC.[41] However, the authors reported a sevenfold increase in CIN and CC when lower serum folate concentration coexisted with HPV infection. This suggests that along with low blood folate, some concurrent factors must be present that will predispose to carcinogenesis. ►**Fig. 2** represents the effects of the availability of folate in body and the risk of CC development.

Folate's possible protection against CC is based on its roles in DNA synthesis and repairing damaged DNA. Folate is involved in DNA methylation, through which it may influence gene expression. If an adequate amount of folate is present, then DNA methylation will occur and proto-oncogenes can be turned off, thus preventing uncontrolled cell growth. However, if there is low folate in the blood, then DNA hypomethylation occurs and genes are turned "on," which increases the risk of uncontrolled cell growth causing cancer.[41]

Vegetables and Fruits

Fruits and vegetables are good sources of antioxidant phytochemicals that mitigate the damaging effect of oxidative stress. Carotenoids are a group of phytochemicals that are responsible for different colors of foods. A wide variety of fruits and vegetables provide a range of nutrients and different bioactive compounds including phytochemicals, vitamins, minerals, and fibers.[42] A large prospective study conducted by the European Prospective Investigation into Cancer and Nutrition involving 299,649 women observed a statistically significant inverse association of ISC (invasive squamous carcinoma) with a 100 g increase in the daily total fruit intake. Their findings revealed that the protective effects of fruits might play a major role in ICC but not in CIN. This suggested that if there was any

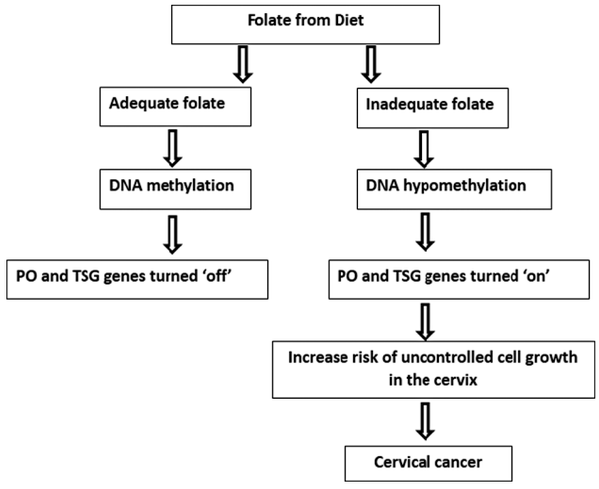

Fig. 2. Availability of folate and the risk of CC development (PO: Protooncogenes; TSG: Tumor Suppressor Genes).

true protective effect, it would be observed in the late stages of the cancer process (ISC> CIN2/3 > CIN1).[43] However, Giuliano et al found a reduced risk of HPV persistence among those with a high consumption frequency of papaya and orange. In their study, intake of fatty foods rich in saturated fatty acid was positively associated with HPV infection probably reflecting participants' lifestyle as these food groups were inversely correlated with fruit intake.[44]

The consumption of green–yellow vegetables rich in beta-carotene (carrot, pumpkin, and green vegetables) showed a reduced risk for CC among all age groups, while that of light-green vegetables (cabbage and lettuce) did not appear to influence the risk.[27] Increased dietary intake of dark green and deep yellow vegetables and fruits, which are important dietary sources of α-carotene, β-carotene, β-cryptoxanthin, and lutein, were negatively associated with CIN3. However, there are growing pieces of evidence that a high intake of foods rich in β-carotene and lutein has an important role in immune response possibly acting against the persistence of HPV infection.[32] All these pieces of evidence suggest that fruits and vegetables provide overall protection against all stages of CC.

Antioxidants present in a variety of vegetables and fruits can act as efficient scavengers of free radicals thereby preventing damage to macromolecules. Free radicals and oxidants if not neutralized by antioxidant molecules, then the inflammatory processes induced by HPV infection would lead to extensive damage to DNA and proteins. Additionally, oxidative stress decreases immune function and increases viral replication. It has been proposed that antioxidants present in fruits and vegetables like vitamin A (retinoic acid), C (ascorbic acid), and E (tocopherol) can prevent HPV persistence and inhibit DNA adduct formation thereby preventing cervical carcinogenesis and proliferation of cancer cells by inducing apoptosis, stabilizing the p53 protein, and reducing immunosuppression.[1,2,10]

Others

There are many other nutrients that play a critical role in CC development like apigenin, genistein, quercetin, sulforaphane, TPPs, PUFA, etc. Apigenin is a flavone present in vegetables such as parsley, celery, chamomile, and Egyptian plant Moringa peregrine. Apigenin can sensitize HeLa cells to paclitaxel-induced apoptosis through the accumulation of excess intracellular ROS. It is considered a mediator for chemoprevention in the cancerous process and induces autophagia by which it exerts its protective role.[12]

Genistein is an isoflavone originating from a number of plants such as lupine, fava beans, soybeans, kudzu, Psoralea, Flemingia vestita, and coffee. Genistein inhibits the enzymes like tyrosine kinase and DNA topoisomerase II that regulate cell division and cell survival.[12] It also decreases cellular viability by induction of apoptosis due to the generation of ROS.[1,2] Additionally, genistein has been found to have anti-angiogenic effects, thereby blocking the uncontrolled cell growth associated with cancer.

Quercetin is a flavonoid ubiquitously present in vegetables and fruits, and its antioxidant effect is implied to be helpful for human health. Sundaram et al reported an antiproliferative, proapoptotic, and antimigratory effect of quercetin on HeLa cells by modulating various signaling pathways.[45] Quercetin induces apoptosis in CC cells mainly by extrinsic pathway. Quercetin was found to alter the expression of several genes involved in PI3K, WNT, mitogen-activated protein kinases (MAPK), JAK/STAT pathways, effectively causing inhibition of cell proliferation, cell cycle arrest, and apoptosis in CC (HeLa) cells. A promising alternate route to cancer chemoprevention and treatment strategies appears to be the use of dietary polyphenols such as quercetin.

Sulforaphane is an organosulfur compound obtained from cruciferous vegetables such as broccoli, brussels sprouts, and cabbages. Sulforaphane acts by delaying the development of CC by arresting cell growth in the G2/M phase[1,2] and inducing apoptosis by upregulation of proapoptotic genes. Sharma et al analyzed the effect of sulforaphane on the expression of Bcl-2, COX-2, and IL-1β by RT-PCR on HeLa cell and reported that sulforaphane was found to induce dose-dependent selective cytotoxicity in HeLa cells in comparison to normal cells pointing to its safe cytotoxicity profile.[46] Also, the expression analysis of genes involved in apoptosis and inflammation revealed significant downregulation of Bcl-2, COX-2, and IL-1β upon treatment with sulforaphane, and it proves that sulforaphane uses its anticancer activities via apoptosis induction and anti-inflammatory properties, which may be useful for the treatment of CC.

EGCG (epigallocateocatechin-3-gallate), a TPP, is the most abundant catechin compound in green tea. Increasing pieces of evidence show that EGCG can be beneficial in treating CCs. Among numerous mechanism studies, EGCG binds and inhibits the antiapoptotic protein Bcl-xl, a protein involved in cancer cell survival. EGCG has shown to inhibit MAPK, cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 and NF-κB, topoisomerase I, and matrix metalloproteinases.[12] TPPs can act in synergy with bleomycin (BLM), thus enhancing its therapeutic properties. TPP-BLM synergistically inhibits CC cell viability by reduced proliferation through apoptosis. Singh et al reported that TPPs such as EGCG and theaflavins (TF) can chemosensitize CC cells (HeLa, SiHa) to cisplatin-induced growth inhibition and apoptosis by excessive ROS generation.[47]

A recent clinical trial by Wuryanti et al concluded that dietary supplementation enriched with PUFA can reduce the inflammatory response in patients with advanced CC. PUFA reduces serum PGE2 levels thereby lowering cancer cell viability. Thus, PUFA supplementation together with radiotherapy enhances the response of CC cells to radiations.[21]

Conclusion

Regarding dietary nutrients, various antioxidants have varying capacities to affect the natural history of HPV-mediated CC. Particularly, each vitamin may have various suppressive effects at various phases of the development of CC (from HPV infection to the development of CIN and CC). The intake of vitamins A and D may prevent the early events in CC development (from HPV infection to CIN 1). Vitamin C and carotenoids have the potency to inhibit the events from HPV infection to the development of

various grades of CIN. However, lycopene carotenoid has been observed to inhibit CIN 3 development. The reason behind such multiple mechanisms of action of carotenoids is unclear. The intake of vitamin E and folate might be more effective for preventing high-grade CIN. Consumption of fruits and vegetables rich in multivitamins may significantly reduce the risk of the overall disease. Polyphenols, flavonoids, and PUFA are often used in CC treatment in combination with chemotherapy and radiotherapy for obtaining better results. Therefore, health care professionals should counsel women with HPV preinfection or infection to boost their intake of dietary antioxidants and to bring changes in their lifestyles like in sexual activity, parity, OC use, and quit smoking, in order to stop CC from developing. There is a further need to take up research on this important aspect of diet as a useful primary prevention strategy.

Contributions

All the authors contributed in literature survey, collection of data, and manuscript writing.

Funding

This research received funding from ICMR.

Conflicts of Interest

None declared.

Acknowledgments

The authors would like to thank the Indian Council of Medical Research (ICMR) for sponsoring this research work and to Vice chancellor, Raiganj University for providing all the facilities to conduct the present research.

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Real-World Outcome of Platinum-Based Chemotherapy in Advanced Breast Cancer (ABC): A Retrospective Study from a Tertiary Cancer Center in India

Indhuja Muthiah Vaikundaraja[1] Manikandan Dhanushkodi[1] Venkatraman Radhakrishnan[1] Jayachandran Perumal Kalaiarasi[1] Nikita Mehra[1] Gangothri Selvarajan[1] Arun Kumar Rajan[1] Siva Sree Kesana[1] Balasubramanian Ananthi[2] Priya Iyer[2] Manjula Rao[3] Arvind Krishnamurthy[3] Sridevi Velusamy[3] Rama Ranganathan[4] Tenali Gnana Sagar[1]

[1] Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[2] Department of Radiation Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[3] Department of Surgical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[4] Department of Epidemiology & Biostatistics, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence Manikandan Dhanushkodi, MD, DM, DNB, Medical Oncology, Cancer Institute (WIA), Chennai, 38, Sardar Patel Road, Chennai, Tamil Nadu, 600036, India (e-mail: dmani1982@gmail.com).

Ind J Med Paediatr Oncol 2024;45:383–389.

Abstract

Introduction There is a paucity of data on platinum-based chemotherapy in advanced breast cancer (ABC) from developing countries like India.

Objectives The objectives were to analyze the efficacy and safety of platinum-based chemotherapy in patients with ABC.

Materials and Methods This was a retrospective study of 35 patients with ABC who were treated with platinum-based chemotherapy (gemcitabine and carboplatin, [GC]) in a tertiary cancer center in India from August 2015 to November 2019. The inclusion criteria were patients with ABC, who had received palliative chemotherapy with GC. The exclusion criteria were patients who had received less than two cycles of GC and patients who received platinum-based chemotherapy for neuroendocrine carcinoma of the breast.

Results The median age was 45 years (range: 28–68 years). All patients were female (97%) except one male (3%). The histology was ductal carcinoma (77%), mixed (17%), and others (6%). Out of the 12 patients tested for breast cancer (BRCA) gene mutation, six patients had a BRCA mutation. Patients with metastatic and locally progressive disease were 91 and 9%, respectively. The median number of prior lines of systemic therapy for metastatic disease was 1 (range: 0–5). The median number of sites of metastasis was 2 (range: 0–5). Patients with visceral crises were 23%. The median number of cycles of GC chemotherapy received was 6 (range: 2–6). A dose reduction in chemotherapy was done in 74%. The responses among 34 evaluable patients were

Keywords
- advanced breast cancer
- platinum-based chemotherapy
- real-world outcome

article published online
December 11, 2021

DOI https://doi.org/10.1055/s-0041-1735597.
ISSN 0971-5851.

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

complete response (11%), partial response (24%), stable disease (41%), and progressive disease (24%). Grade 3 or more hematological and nonhematological toxicities were observed in 69 and 9%, respectively. The median progression-free survival and overall survival were 6 and 8 months, respectively. The 1-year progression-free survival and overall survival were 19 and 34%, respectively. Multivariate analysis showed that patients who had received more than 3 cycles had a better outcome.

Conclusion GC was an active and well-tolerated regimen in ABC regardless of the receptor status. Further prospective randomized studies are warranted to assess the optimal regimen in patients with triple-negative breast cancer.

Introduction

Platinum-based neoadjuvant chemotherapy (cisplatin and carboplatin) has been shown to improve pathological complete response in triple-negative breast cancer (TNBC), especially in the breast cancer (BRCA) mutant subtype.[1] Platinum-based chemotherapy (PBC) can be combined with anti-HER2 therapy (trastuzumab) for the treatment of HER2-positive BRCA.[2] The impact of PBC as compared to non-PBC in advanced breast cancer (ABC) is unclear. The chemotherapy drugs that can be combined with platinum include taxane, vinorelbine, etoposide, and gemcitabine.[3] The response rates are higher in the first line as compared to second or third-line therapy.[4] There is a paucity of data on PBC in ABC from developing countries like India. The objectives of this study were to analyze the efficacy and safety of PBC in patients with ABC.

Materials and Methods

This was a retrospective study of 35 patients with ABC who had received palliative chemotherapy with gemcitabine and carboplatin (GC) in a tertiary care cancer center from August 2015 to November 2019. The data were retrieved from the electronic medical records (EMR) of these patients for whom gemcitabine and carboplatin prescription was given. At our hospital, patient records registered from 1954 until 2016, and records of patients who had deceased were scanned. The data of patients for whom case records were scanned were obtained from the EMR. For the alive patients registered after 2016, we obtained data from the individual case record obtained from the tumor registry.

The inclusion criteria were patients with ABC, who had received palliative chemotherapy with GC. The exclusion criteria were patients who had received less than two cycles of GC and patients who received PBC for neuroendocrine carcinoma of the breast. BRCA was tested as per National Comprehensive Cancer Network (NCCN) hereditary BRCA testing criteria[5] and the methodology used was Ion Torrent next-generation sequencing. The primary objective was to assess the progression-free survival (PFS) and overall survival (OS) of patients with recurrent/metastatic BRCA who received palliative chemotherapy with GC while the secondary objective was to assess the toxicity.

Prechemotherapy blood investigations included hemogram, renal function test, and liver function test before the day (D) 1 of each cycle and hemogram and differential count before D8 of each cycle. Chemotherapy was initiated only if the absolute neutrophil count was more than 1000/μL and platelet count was >1 lakh/μL. The premedications were injection palonosetron 0.25 mg intravenous bolus and injection dexamethasone 12 mg intravenous bolus 30 minutes before chemotherapy. The chemotherapy schedule was injection gemcitabine 1 gm/m^2 in 250 mL 0.9% normal saline over 30 minutes intravenously on D1 and D8 and injection carboplatin area under the curve 5 or 6 in 250 mL 0.9% normal saline over 1 hour on D1.

Patients were assessed clinically for response and toxicity before each cycle. Imaging was done with either chest X-ray, ultrasound of abdomen/pelvis, or contrast-enhanced chest tomography of chest/abdomen/pelvis or positron imaging tomography-computed tomography once every 3 to 4 months and when clinically indicated. Responses were assessed as per the Response Evaluation Criteria in Solid Tumors, version 1.1 criteria.[6] Toxicity was graded as per Common Terminology Criteria for Adverse Events, version 4.0.[7] Chemotherapy dose reduction was done in patients with $\geq$ grade 3 toxicity and discontinued in patients with life-threatening toxicity.

Statistical Analysis

Descriptive statistics were used to analyze the baseline characteristics. PFS was calculated from the date of initiation of GC to the date of recurrence or death. OS was calculated from the date of the initiation of GC to the date of death due to any cause. Survival was estimated by the Kaplan–Meier method and compared across groups using the log-rank test. Cox proportional hazard model was used to find the prognostic factors affecting the outcome. All *p*-values were two-sided, and values <0.05 were considered significant. This was performed using the Statistical Package for the Social Sciences version 15 (SPSS), Chicago, Illinois, United States.

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 Institutional

Ethics Committee of Cancer Institute (WIA), Chennai (IEC/2020/Aug 08), dated Aug 14, 2020 and a waiver of consent was obtained as this was a retrospective study.

Results

Baseline Characteristics

A total of 35 patients were included in this analysis with a median follow-up of 8 months (range: 2–39 months). The median duration from diagnosis to start of GC chemotherapy was 18 months (range: 2–113 months). The median age was 45 years (range: 28–68 years). All patients were females ($n = 34/35$, 97%) except for one male ($n = 1/35$, 3%). Premenopausal women were 76% ($n = 26/35$) and the rest 24% ($n = 8/35$) were postmenopausal. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 1 (83%) and 2 (17%). The histology was ductal carcinoma (77%), mixed (17%), and others (6%). The differentiation was grade 2 (17%) and grade 3 (80%). The molecular subtype was luminal B ($n = 10/35$, 29%), HER2 positive ($n = 6/35$, 17%), and triple-negative subtype ($n = 19/35$, 54%). Two of the six patients with HER2-positive BRCA had received adjuvant trastuzumab. Out of the 12 patients tested for BRCA 1 and 2 gene mutations, six patients had a BRCA 1 mutation. Recurrence was confirmed by biopsy in 37% ($n = 13/35$) patients. Patients with metastatic and locally progressive disease were 91 and 9%, respectively. The median number of prior lines of systemic therapy for metastatic disease was 1 (range: 0–5). The median number of sites of metastasis was 2 (range: 0–5). Patients with visceral crises were 23% ($n = 8/35$). This study included two patients with brain metastasis and one with choroidal metastasis. The baseline characteristics are shown in ►**Table 1**.

Table 1 Baseline characteristics ($n = 35$)

Variable	Number (%)
Median age	45 years (range: 28–68 years)
Sex	
Female	34 (97)
Male	1 (3)
Menopausal status[a]	
Premenopausal	26 (76)
Postmenopausal	8 (24)
Comorbid illness[b]	
Diabetes mellitus	9 (27)
Hypertension	7 (21)
Others	8 (24)
None	18 (54)
ECOG performance status	
0	0 (0)
1	29 (83)
2	6 (17)
3 or 4	0 (0)
Histology	
Infiltrating ductal carcinoma	27 (77)
Mixed	6 (17)
Others[c]	2 (6)
Differentiation	
Grade 1	0 (0)
Grade 2	6 (17)
Grade 3	28 (80)
Unknown	1 (3)
Estrogen receptor	
Positive	13 (37)
Negative	22 (63)
Progesterone receptor	
Positive	8 (23)
Negative	27 (77)
HER2	
Positive	6 (17)
Negative	28 (80)
Unknown	1 (3)
Molecular subtype	
Luminal A (ER/PR positive, HER2 negative & Ki 67 $\leq$ 20%)	0 (0)
Luminal B, HER2 negative (ER/PR positive & Ki 67 $>$ 20%)	10 (29)
HER2 positive	6 (17)
TNBC	19 (54)

(*Continued*)

Treatment, Response, and Toxicity

The median number of cycles of GC chemotherapy received was 6 (range: 2–6). A dose reduction in chemotherapy was done in 74% ($n = 26/35$). The responses were complete response ($n = 4/35$, 11%), partial response ($n = 8/35$, 23%), stable disease ($n = 14/35$, 40%), progressive disease ($n = 8/35$, 23%), and unknown ($n = 1/35$, 3%). The hematological and nonhematological toxicities of $\geq$ grade 3 were observed in 69 and 9%, respectively. Grade 3 or more anemia, leucopenia, and thrombocytopenia were observed in 34, 46, and 37%, respectively. Febrile neutropenia was observed in 9% of patients. Grade 3 or more chemotherapy-induced nausea and vomiting, hypersensitivity, and neuropathy were observed in 3, 3, and 3%, respectively. There was no treatment-related mortality.

Survival

The median PFS (►**Fig. 1**) and OS (►**Fig. 2**) were 6 (95% confidence interval [CI]: 3.2–5.7 months) and 8 months (95% CI: 5.3–10.7 months), respectively. The 1-year PFS and OS were 19 and 34%, respectively. Univariate analysis was done with factors including age, menopausal status, histology, molecular subtype, BRCA status, number of lines of prior therapy, number of sites of metastasis, and number of cycles

Table 1 (*Continued*)

Variable	Number (%)
BRCA mutation status	
BRCA 1 or 2 mutation present	6 (17)
Wild type	6 (17)
Unknown	23 (66)
De novo metastatic disease	12 (35)
Recurrent disease	23 (65)
Median number of sites of metastatic disease	2 (range: 0–6)[d]
Visceral crisis	
Yes	8 (23)
No	27 (77)
Median number of lines of prior therapy in metastatic disease	1 (range: 0–5)

Abbreviations: BRCA, breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.
[a]One male patient was excluded.
[b]Percentage may not add to 100% as patients had combination of comorbid illness.
[c]One patient has metaplastic carcinoma and 1 patient had poorly differentiated carcinoma with neuroendocrine features.
[d]Range starts with 0 as 3 patients had only locally progressive disease.

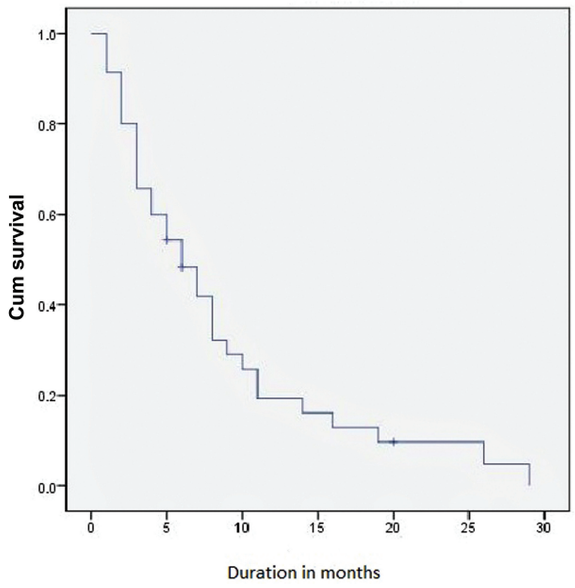

Fig. 1 Kaplan–Meier curve (x-axis: survival in months; y-axis: percentage of patients) of 35 patients with advanced breast cancer treated with gemcitabine–carboplatin showing a median progression-free survival of 6 months (95% confidence interval: 3.2–5.7 months).

of GC chemotherapy for correlation with PFS. Univariate analysis showed that patients with infiltrating ductal carcinoma histology and those who received more than 3 cycles of chemotherapy had better PFS (►**Table 2**). Multivariate analysis confirmed that patients who had received more than three cycles of chemotherapy had better PFS (hazard ratio: 3.05, 95% CI: 1.36–6.82, $p = 0.007$).

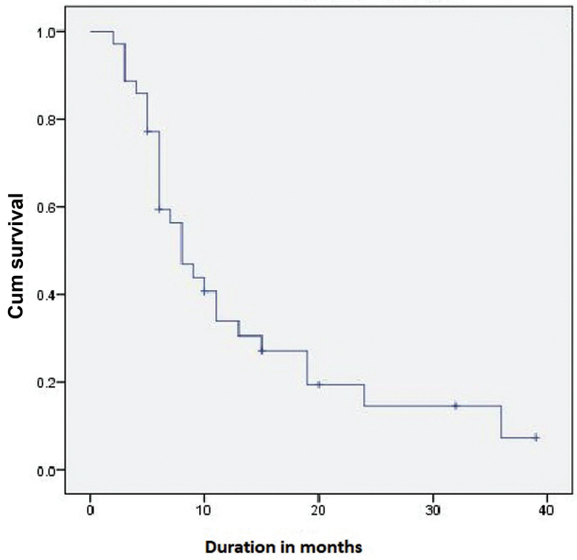

Fig. 2 Kaplan–Meier curve (x-axis: survival in months; y-axis: percentage of patients) of 35 patients with advanced breast cancer treated with gemcitabine-carboplatin showing a median overall survival of 8 months (95% confidence interval: 5.3–10.7 months).

Discussion

This study is the largest study from India on PBC in ABC. The study included real-world patients like those in ECOG PS 2 (17%), HER2 positivity (17%), and pretreated (maximum 5 lines of prior systemic therapy) ABC who were treated with gemcitabine and carboplatin.

Currently, there is no standard chemotherapy option in patients who progress after exposure to anthracycline, taxane, and capecitabine. The chemotherapy options include ixabepilone, vinorelbine, eribulin, and PBC. We chose GC as it was an affordable treatment option.

Germline BRCA testing was done in 12 patients. Among them, 6 patients (50%) had BRCA 1 mutation and none had BRCA 2 mutation. The NCCN guidelines recommend BRCA testing for all patients with a family history of breast or ovarian cancer, age less than 45 years, bilateral BRCA, male BRCA, breast and ovarian cancer, and TNBC less than 60 years of age.

Biopsy confirmation of recurrent disease was done only in 37% due to inaccessible site, patient's unwillingness, and short disease-free survival. All current guidelines including (NCCN), American Society of Medical Oncology, European Society of Medical Oncology, and ABC recommend repeat biopsy from accessible metastatic setting especially in the first recurrence. Repeat biopsy is useful as it not only confirms the recurrence but also identifies discordance in ER, PR, and HER2 status that can alter systemic therapy.[8] Studies from All India Institute of Medical Sciences, Delhi and Kidwai, Bengaluru have shown a receptor (ER/PR/HER2)

Table 2 Univariate analysis with correlation with progression-free survival

Variable	HR	CI (95%)	*p*-Value
Histology			
Infiltrating ductal carcinoma	1.00		
Others	2.40	1.04–5.67	0.04
Molecular subtype			
Luminal B	1.00		
HER2 enriched	1.23	0.33–4.60	0.75
Triple negative breast cancer	1.76	0.79-3.92	0.16
Number of cycles of chemotherapy			
$>$ 3 cycles	1.00		
$\leq$ 3 cycles	3.23	1.47–7.06	0.03
Number of sites of metastatic disease			
$\leq$ 2 sites	1.00		
$>$ 2 sites	0.88	0.39–1.99	0.76
Number of lines of prior systemic therapy for metastatic disease			
$\leq$ 2 lines	1.00		
$>$ 2 lines	0.46	0.16–1.35	0.16
BRCA mutation			
BRCA positive	1.00		
BRCA wild type	0.43	0.10–1.78	0.25

Abbreviations: BRCA, breast cancer; CI, confidence interval; HR, hazard ratio.

discordance of 10 to 20% in recurrent BRCA and can be useful in treatment decisions.[9,10]

A Cochrane database systematic review ($n = 9742$) showed that combination chemotherapy had improved response and survival but with increased toxicity.[11] But another Cochrane database systemic review ($n = 2317$) showed no difference in OS in patients receiving combination versus sequential single-agent chemotherapy.[12] Currently, we do not have studies comparing GC to carboplatin alone in advanced BRCA.

In our study, dose reduction with GC chemotherapy was seen in 74%. A phase 2 study showed that dose reductions with GC occurred in 60% due to myelosuppression.[13] Although dose reduction happened in two-thirds of the patients, most patients completed all the six cycles of chemotherapy.

A study from Gujarat Cancer Research Institute in 21 patients with TNBC showed a response rate of 72% and the survival details were unreported.[14] There are no further studies on PBC in ABC from India. Our study had a lower overall response rate (34%) as it included pretreated patients with ABC. A retrospective study of patients ($n = 375$) with de novo ABC from All India Institute of Medical Sciences, Delhi, showed that hormone-positive subset, good PS (0-1), and oligometastasis had a better outcome. Patients with TNBC and those with liver or brain metastasis had a poor outcome.[15]

A study from Royal Marsden showed that PBC improved response and PFS but not OS in patients with advanced TNBC.[16] The triple-negative (TNT) randomized controlled trial (RCT) in patients with untreated TNBC, carboplatin, and docetaxel had similar response and survival. But in patients with BRCA mutated TNBC, carboplatin had a better response and survival.[17] A phase 3 RCT from China showed that patients treated with GC had a better PFS than gemcitabine-paclitaxel in untreated advanced TNBC.[18] A meta-analysis with three RCTs showed that PBC does not improve PFS in patients with advanced TNBC.[19] Another meta-analysis of 4,625 patients with ABC showed that PBC improved PFS and OS with increased fatigue, hematological, and gastrointestinal toxicity.[20] The details of the studies with PBC in ABC are shown in ►**Table 3**.

In our study, the median PFS and OS were only 6 and 8 months, respectively. This could be due to the inclusion of real-world patients like heavily pretreated subset and HER2-positive patients (who could not afford anti-HER2 therapy). The TNBC and BRCA mutant subtype did not correlate with survival possibly because of the small numbers. GC-based regimen could be considered as first-line regimen in patients with BRCA mutant advanced TNBC and as a third-line regimen after anthracycline and taxane in patients with BRCA wild-type advanced TNBC.

Poly ADP ribose polymerase (PARP) inhibitors (olaparib, talazoparib) had shown to improve response and PFS as compared to non-PBC (capecitabine, eribulin, or vinorelbine) in patients with germline BRCA-mutated advanced BRCA.[21,22] However, the addition of PARP inhibitor (iniparib) to GC chemotherapy did not improve survival in patients with advanced TNBC.[23]

Immunotherapy (atezolizumab) with nab-paclitaxel had shown to improve survival as compared to nab-paclitaxel alone in patients with untreated advanced TNBC, especially the PD-L1-positive subset.[24] Pembrolizumab with chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine + carboplatin) improved PFS as compared to chemotherapy alone in patients with PD-L1-positive (combined positive score $\geq$ 10) untreated advanced TNBC. Sacituzumab govitecan-hziy is an antibody-drug conjugate that targets the human trophoblast cell-surface antigen 2 (Trop-2) with SN-38 had shown durable responses in patients with heavily pretreated advanced TNBC.[20]

The multivariate analysis showed that patients who received more than three cycles of chemotherapy had an improved PFS. None of the other studies of PBC in ABC had shown a similar correlation. The strength includes the first study with the largest sample size from India on real-world outcomes with PBC in ABC. The limitations include retrospective design, lack of biopsy confirmation of recurrence (63%), and unknown BRCA status (66%). Further prospective randomized studies are warranted to assess the optimal regimen in patients with TNBC.

Table 3 Studies on platinum-based chemotherapy in advanced breast cancer

Study	Inclusion criteria	Sample size	Design	Response (%)	PFS (mo)	OS (mo)
Our study	ABC	35	Retrospective	34	6 mo	8 mo
Maka et al[14]	TNBC	21	Retrospective	72	–	–
Sirohi et al, UK[9]	TNBC	155	Retrospective	41	6 mo	11 mo
Tutt et al, TNT trial[10]	TNBC	766	Phase 3, RCT, carboplatin versus docetaxel	31 versus 34%	3.1 mo versus 4.4 mo	12.8 mo versus 12 mo
Hu et al. China[11]	TNBC	240	Phase 3, RCT, gemcitabine cisplatin versus gemcitabine paclitaxel	65 versus 49%	7.7 mo versus 6.4 mo	Immature

Abbreviations: ABC, advanced breast cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; TNBC, triple-negative breast cancer.

Conclusion

This study is the largest study from India on PBC in ABC representing the real-world outcome. Patients with ECOG PS 2, HER2 positivity, and pretreated ABC were included in this analysis. GC was an active and well-tolerated regimen in advanced BRCA regardless of the receptor status.

Presentation

This study has not been presented in any meeting.

Registration Number

Not applicable as it is not a clinical trial.

Authors' Contribution

Conception (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi)/acquisition (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi)/analysis (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi, Venkatraman Radhakrishnan, Jayachandran Perumal Kalaiarasi, Nikita Mehra, Arun Kumar Rajan, Gangothri Selvarajan, Siva Sree Kesana, Balasubramanian Ananthi, Priya Iyer, Manjula Rao, Arvind Krishnamurthy, Sridevi Velusamy, Rama Ranganathan, Tenali Gnana Sagar). All authors made substantial contribution toward drafting and final approval and agreed to be accountable on all aspects of the manuscript.

Source of Funding

None declared.

Conflict of Interest

None declared.

Acknowledgement

None declared.

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A Pilot Study Conducted at a Tertiary Cancer Care Center, Evaluating the Serum Asparaginase Activity in Children Suffering from Acute Lymphoblastic Leukemia after the Administration of Biosimilar Pegaspargase

Archana Melavarige Venkatagiri[1] Vasudeva K. Bhat[1] Arjun Asok[2] Krishnananda Prabhu[2]

[1] Department of Pediatric Hematology and Oncology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Karnataka, India
[2] Department of Biochemistry, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Karnataka, India

Address for correspondence Vasudeva Bhat K., MD, DM, Division of Pediatric Hematology and Oncology, Kasturba Medical College, Manipal Comprehensive Cancer Care Centre, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India (e-mail: vasudev.bhat@manipal.edu).

Ind J Med Paediatr Oncol 2024;45:390–395.

Abstract

Introduction L-asparaginase is considered to be the most important component in the treatment of acute lymphoblastic leukemia (ALL). Intensifying the use of L-asparaginase during treatment for ALL has resulted in a significant rise in the percentage of children and adolescents who are cured of the disease. Asparaginase trough activity more than or equal to 100 IU/L on day 7 has been found to be the desired activity level in all childhood leukemia patients.

Objectives Due to the paucity of data on biosimilar pegaspargase in the upfront setting, we planned this prospective pilot study to evaluate the levels of serum asparaginase activity (SAA) after biosimilar pegaspargase infusion.

Materials and Methods It is a prospective, single-center, pilot study of 10 pediatric ALL patients for the duration of 6 months. All children less than 18 years with ALL on treatment with curative intent and receiving pegaspargase and who provided informed consent were included in this study. The enzymatic spectrophotometric method was used to determine SAA, and it was measured on the 7th and 14th days after the first dosage of pegaspargase-asparaginase, as well as on the 14th day after the second dose of pegaspargase-asparaginase, while toxicity was charted according to **Common Terminology Criteria for Adverse Events** (CTCAE) version 4.0.

Results From 10 patients with a median age of 5.5 years, a grand total of 29 samples were taken for analysis. Children who received pegaspargase had either B-ALL or T-ALL. After the first dose, mean ± SD (standard deviation), SAA levels at day 7 was 131.3 ± 38 IU/L and at Day 14 was 94.8 ± 8 IU/L. After the second dose, mean ± SD SAA level at day 14 was 86.1 ± 15 IU/L. No patient had clinical hypersensitivity reaction and no patient reported any asparaginase-related toxicity. One patient died due to sepsis, infection with multidrug-resistant gram-negative bacteria.

Keywords
- pegaspargase
- acute lymphoblastic leukemia
- serum asparaginase activity
- childhood leukemia

article published online
September 18, 2023

DOI https://doi.org/10.1055/s-0043-1774806.
ISSN 0971-5851.

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

Conclusions Biosimilar pegaspargase maintained good SAA levels 7 and 14 days after infusion.

Drug Trial Registration: Clinical Trial Registry of India vide reference CTRI/2021/08/036033 and available at https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=59285&EncHid=&userName=

Introduction

Acute lymphoblastic leukemia, also known as ALL, is an extremely rare form of hematologic malignancy that is characterized by an increase in the production of abnormal lymphoid progenitor lymphoblast cells. These cells can be either B cells or T cells. ALL is more prevalent in children, making up nearly 30% of all cases of pediatric cancer, while only accounting for 1% of all cases of adult cancer. When taking into account the effects of age, 5-year overall survival rate for children is greater than 90%, while it is less than 20% for older adults.[1–3]

L-asparaginase is the pivotal drug used in the treatment of ALL. The patients who have been diagnosed with ALL are given *Escherichia coli* in either its native form or in conjugation with poly(ethylene glycol) (PEG) as their treatment. Reference biologic pegaspargase is the approved first-line asparaginase treatment for pediatric ALL. *E. coli* is PEGylated by reacting with either succinimidyl carbonate PEG (calaspargase pegol) or succinimidyl succinate PEG (biologic pegaspargase). L-asparaginase uses the substrate l-asparagine (Asn) to catalyze the production of free l-aspartic acid (Asp). The main goal of l-asparaginase therapy is to lower or eliminate endogenous circulating l-asparagine from the blood, depriving circulating blast cells of this crucial nutrient. PEG incorporation, on the other hand, increases steric hindrance, which restricts access of circulating peptidases and proteases and significantly lengthens half-life. This also lessens its immunogenicity; however, compared with the more than 30% incidence rate as observed with native enzyme, pegaspargase is only used in 3% of first-line and 10% of relapsed ALL patients without any prior reactions. Patients' immune systems can still produce antibodies against the linker.[1]

Intensification of L-asparaginase during therapy has led to dramatic increase in cure rates. Asparaginase trough activity more than or equal to 100 IU/L on day 7 has been found to be the desired activity level. Biologic pegaspargase (Oncospar) is not easily available in India, while other biosimilar pegaspargase is expensive compared with native formulations. Biosimilar native L-asparaginase have shown poor activity in pilot study.[4]

Serum asparaginase activity (SAA) has developed into a valid pharmacodynamic tool because there is a direct correlation between the level of L-asparaginase activity and decrease in asparagine concentration. Following a 1981 study that showed plasma and cerebrospinal fluid (CSF) asparagine were undetectable at this level, which was later validated in numerous studies, SAA 0.1IU/mL was proposed as the minimum desired threshold for meaningful efficacy.[1,3] Therefore, SAA that reflects the enzyme's ability to deplete asparaginase should be compulsorily monitored in every pediatric ALL patients. Comparisons should be included in prospective work and identification of new microbiological sources of L-asparaginase to maximize the clinical efficacy of the drug while minimizing the side effects.[1,5]

Forty-six B-ALL patients who had relapsed were randomly assigned to receive pegaspargase (2500 IU/m^2) either weekly (four doses) or biweekly (two doses) during reinduction in the POG 9310 study. The overall complete response (CR) rate was 90%, and the cohort receiving weekly (97%) rather than biweekly (82%) dosing experienced higher CR, $p = 0.003$. Asparaginase activity was more active when the CR rate was higher ($p = 0.012$).[1,6]

In this pilot study, we have inducted biosimilar pegaspargase as the intensification therapy followed by comparing assays at different intervals after first and second dose to keenly observe the trough activity; desired level is more than or equal to 100 IU/L on day 7 so that any needful changes can be met with the existing regimens.

Materials and Methods

It is a prospective, single-center pilot study done at tertiary cancer care center by the Division of Pediatric Haematology and Oncology Manipal Comprehensive Cancer Care Centre and Department of Biochemistry. The duration of this study was 6 months.

Inclusion and Exclusion Criteria

All children less than 18 years of age with ALL on treatment with curative intent and receiving pegaspargase who provided informed consent were included in this study of 6 months duration. However, any child with ALL with Down syndrome was excluded from this study as per the exclusion criteria.

All the patients were administered two doses of biosimilar pegaspargase (manufactured by Indian Pharmaceutical company) intravenously (IV) with a gap of 14 days in between. Assent form along with legally authorized representative form was obtained by subjects' parents or guardians.

Primary and Secondary Outcome

The primary outcome of the study was to measure the trough level activity of peg L-asparaginase at the decay stage at

7 days and 14 days after first dose and 14 days after second dose. While the secondary outcomes in terms of clinical hypersensitivity and asparaginase-related toxicity were measured at day 35 and for more clinical significance to the descriptions of grades, the toxicity charting was done as per the guidelines of Common Terminology Criteria for Adverse Events (CTCAE) V 4.0 for which the grading scale also includes a quantitative component.

Statistical Analysis

Descriptive statistics were used to evaluate the data, including percentages and frequencies for demographic parameters, and median for laboratory parameters and lastly mean and standard deviations for SAA values. Statistical analysis was done using Microsoft Excel. SAA being the key observation estimated using enzymatic spectrophotometric method. Other hematological parameters, which were accounted for, included hemoglobin, platelet count, total bilirubin and direct bilirubin with values taken before first and second dose as part of routine blood tests taken prior to chemotherapy.

Spectrophotometric Estimation of L-Asparaginase Activity

The activity of SAA was estimated by quantifying the levels of Indoxine generated after the substrate L-asparagine in the presence of 8-hydroxyquinolone (Indoxine method).

Standards for the assay were prepared in pooled plasma obtained from the blood bank. A total of seven standard concentrations were decided based on the dosage administered to the patients (2, 1, 0.5, 0.25, 0.125, 0.06, 0.03 IU/mL). The standard curve was plotted using the software mycurvefit.com (►**Fig. 1**). The patient samples were treated the same way as the standards and the optical density (OD) values were plotted against the standard using the same software.

Results

Ten children with B-ALL (7 patients) and T-ALL (3 patients) were included in the study, and 29 samples were collected (►**Table 1**).

After the first dose, mean ± SD (standard deviation) levels of asparaginase on day 7 and 14 were 131.3 ± 38 IU/L and 94.8 ± 8 IU/L followed by mean value of 86.1 ± 15 IU/L on day 14 after the second dose (►**Fig. 2**). Furthermore, in the linear graph, the L-asparaginase activity can be seen well above the expected value and in the 14th day evaluation, the trough levels seem to fall below 100IU/L in certain patients after first dose and in most patients after the second dose. No case of clinical hypersensitivity reported. Asparaginase-related toxicity that includes any thromboembolic event, seizures, vomiting, pancreatitis, encephalitis, and hyperglycemia was not observed in any patient. However, sepsis/febrile neutropenia reported in nine out of ten patients and one patient died due to infection- multidrug-resistant (MDR) gram-negative sepsis. Another study concluded that *Pseudomonas aeruginosa* and *Klebsiella* species were the most frequently isolated organisms, of which most were gram-negative organisms while few were fungal. However, the antibiotic response was good with only some episodes requiring a third-line antibiotic.[7]

Discussion

In 1994, Food and Drug Administration first approved pegaspargase for use in the treatment of ALL patients who were hypersensitive to native forms of L-asparaginase.[8] Asparaginase's tumor-inhibitory properties were discovered nearly 50 years ago when researchers noticed that lymphoma-bearing mice treated with guinea pig serum quickly underwent complete regression. This observation later led to the isolation of asparaginase of bacterial origin.[9]

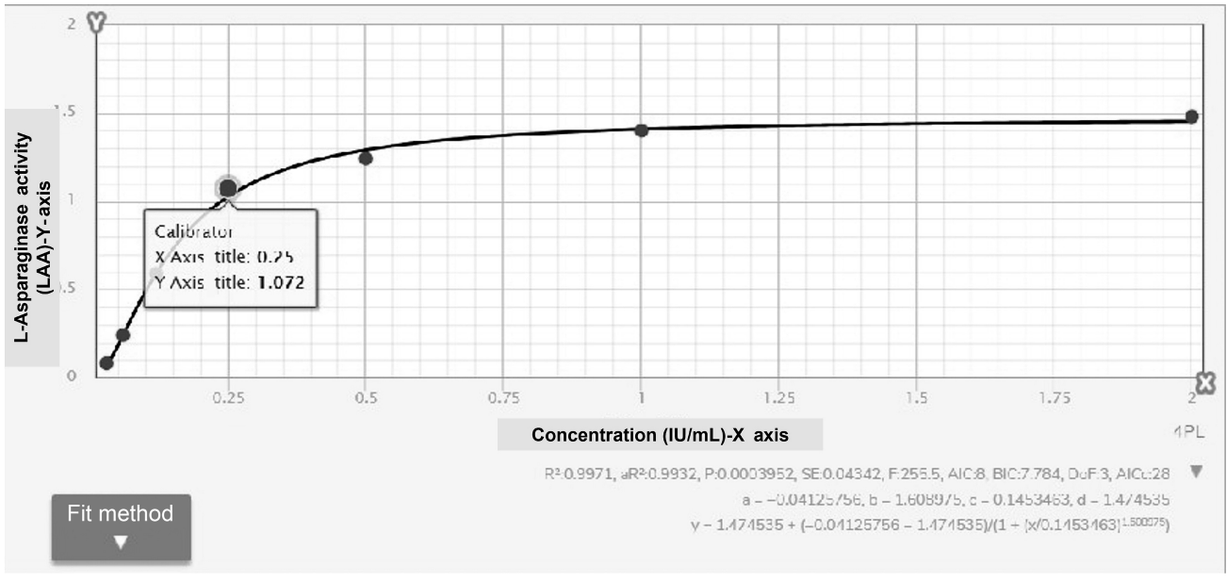

Fig. 1 Standard curve plotted for spectrophotometric estimation of L-asparaginase activity.

Table 1 Demography and laboratory parameters before pegaspargase-L-asparaginase dose

Demography		
Age in years (Median)		5.5
Gender n (%)	Male	5 (50%)
	Female	5 (50%)
Diagnosis	B-cell acute leukemia	7 (70%)
	T-cell acute leukemia	3 (30%)
Laboratory parameters		
	Prior to 1st dose (median)	**Prior to second dose (median)**
Hemoglobin (g/dL)	12.1	9.75
Platelet count (10^9/L)	110	128
Total bilirubin (mg/dL)	0.585	1.01
Direct bilirubin (mg/dL)	0.145	0.34
Albumin (g/dL)	4	3.2

In this pilot study of 10 ALL patients, all were given biosimilar pegaspargase through IV route.[10] In a comparative study, comparison of IV versus intramuscular [IM] route of administration of pegaspargase, Children's oncology group [COG] leukemia 51 trials (2003–2015), the rate of grade 3 hypersensitivity reaction was 3.2% for IV administration whereas it was 5.4% with IM route. Increased IV infusion time of 10% pegaspargase over the first hour and the remaining 90% over the second hour can further reduce the infusion reaction caused by pegaspargase.[8] In the induction stage, the dosage used was 2500 IU/m^2. The administration of IM and IV doses of pegylated *E. coli* asparaginase and Erwinia asparaginase is authorized.[10]

Up to 44 to 60% of patients may develop antiasparaginase neutralizing antibodies in response to bacterial-derived asparaginases, which can inhibit a specific enzyme's activity and prevent the target amino acid from being deaminated within the serum. There is evidence of immunological cross-reaction between the antibodies in various formulations of native *E. coli*-asparaginase and PEG-asparaginases, as suggested by laboratory preclinical findings, but not in Erwinia asparaginase. Due to the liver's involvement in de novo Asn biosynthesis, the pharmacodynamic analyses strongly suggest that more than or equal to 90% of the glutamine must be deaminated before optimal asparaginase deamination can occur.[10]

Enzymes as therapeutic drugs, however, have drawbacks related to the purity of bacterial proteins and the limited pharmacokinetic (PK) distribution in the central compartment of the plasma volume, as well as the potential to induce immunogenicity in the host. Extensive purification is always required to minimize the immune reactions as these proteins also have limited biodistribution in circulation followed by

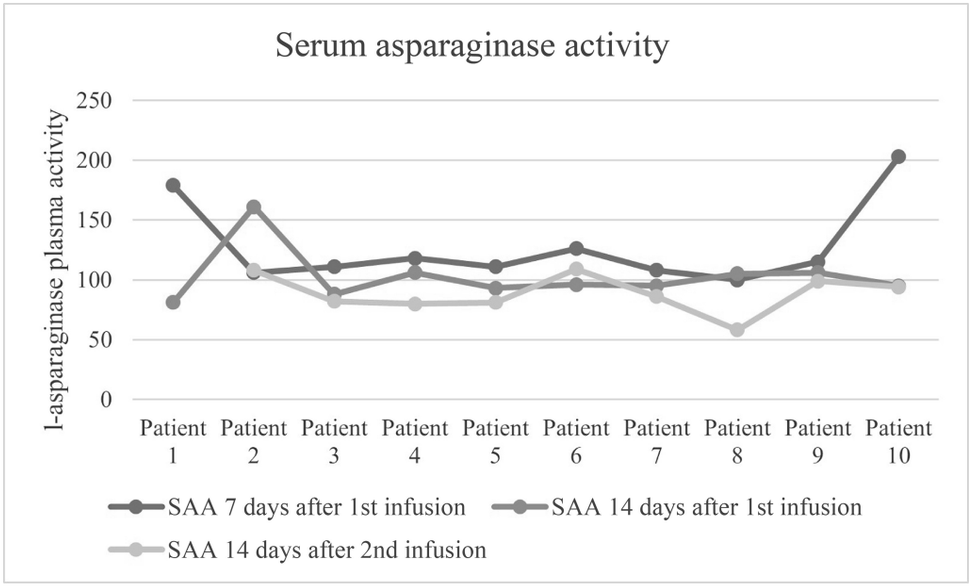

Fig. 2 Serum asparaginase activity (SAA) after first and second infusion of pegaspargase-L-asparaginase.

rapid elimination.[9] The approximate level of Asn in the serum is 50 µM that is de novo synthesis derived from the liver by catalysis of Asp and glutamine.[9] The development of clinical hypersensitivity with the native form is nearly 3 to 78%. Clinical allergy is most commonly seen in asparaginase therapy when initiated without steroids and would be limited if preinduction with the steroid immunosuppression is done pre-emptively resulting in greater Asn depletion and improved outcomes.[9] For prevention of hypersensitivity reactions, in a study, the administration of IV pegaspargase and premedication containing acetaminophen, hydrocortisone,and diphenhydramine was advised.[8] To counter the immunogenicity and the rapid decline, PEG is conjugated to native L-asparaginase thereby increasing the elimination half-life.[9]

Pegaspargase has an approximately 6-day elimination half-life, which is five times longer than native *E. coli* and nine times longer than Erwinia ASNase.[11] Another study found that PEG Asparaginase could lower the frequency of administration because it has a longer half-life (7 ± 2 days) than *E. coli* L-Asparaginase (20 hour).[12] Asparaginase activity as low as 0.05 IU/mL has been reported by several researchers to cause Asn depletion or positive outcomes in patients, challenging the strict 0.1 IU/mL requirement. The target level of plasma asparaginase activity to be attained has been set between 0.05 and 0.4 IU/mL, despite the fact that this range is necessary to achieve sufficient Asn depletion. However, data indicate that a level of 0.02 IU/mL should be maintained for effective plasma asparaginase activity. Pegaspargase clearance is observed to be multiphasic, with a rapid decline during the first day, a slower decline during days 1 to 7, a still slower decline during the second week, and then an increasingly more rapid decline at 22 to 29 days. The activity might fall below 0.02 IU/mL, showing a considerable acceleration of clearance after day 21.[13]

Pegaspargase 2,500 IU/m^2 was administered once or twice weekly in a study for the treatment of ALL. It was found that the trough serum enzymatic activity levels averaged 750 to 800 IU/L at trough times, or on day 7, and increased to higher concentrations of 1,200 to 900 IU/mL on days 21 and 28 post-induction, or after the third and fourth doses, respectively. Additionally, during induction, serum Asn was markedly decreased ($p < 0.002$ for all comparisons) from day 0 to days 7, 14, 21, and 28.[9]

In our study, the trough level was maintained above 100 IU/L post a week of medication that dropped down to a mean level of 94.8IU/L and further to 86.1IU/L at the end of 2 weeks post second dose. Moreover, the percentage of samples with adequate ASNase activity on day 21 of delayed intensification above 0.03 IU/mL were 95 and 31% in pegylated and native, respectively; furthermore above 0.1 IU/mL, it was 95 and 19%, respectively.[14] In the secondary outcome, nine out of ten patients reported sepsis/febrile neutropenia and there was one fatality due to infection—MDR gram-negative sepsis—while no other major events were reported for this duration.

Studying the correlation between SAA and Asn concentration is crucial because the main goal of asparaginase therapy is to deplete serum Asn. However, it has been debatable to measure Asn in the presence of asparaginase due to rapid ex vivo hydrolysis. Although the ideal asparaginase depletion level and duration for leukemic cell death are unknown, several studies legitimately identify a target asparaginase activity level of 100 IU/L.[10] There are some studies that contradict the strict 0.1 IU/mL criteria, such as the Avramis and Panosyan study, which contend that asparaginase activity levels of more than 0.4 to 0.7 IU/mL are necessary for the best asparaginase depletion.[11] According to a recent study, however, an activity level of 20 IU/L can efficiently deplete plasma asparagine, and the 95% confidence interval for plasma asparagine depletion following a pegaspargase dose is close to 22 to 29 days. In line with this information, this pilot study's patients maintained SAA levels above 100 IU/L at 7 days and above 20 IU/L at 14 days, resulting in all patients remaining in remission.[13]

Since it is known that patients with antiasparaginase antibodies have higher asparaginase clearance, there were some restrictions on the number of patients in our pilot study. Additionally, antibody titer was not assessed.[9] PEG Asparaginase was used in our study as the first-line therapy for the diagnosis and management of children with ALL, as recommended by the Chinese guidelines. By the analysis of the collected data, lower hypersensitivity rate and hepatic injury have been shown in the patients of the PEG Asparaginase groups. Additionally, the use of PEG Asparaginase in pharmacotherapy may lessen the financial burden associated with using medical resources because of decreased administration frequency and a shorter length of hospital stay.[12]

Levocarnitine and vitamin B complex are being tested in numerous ongoing studies for their ability to treat hyperbilirubinemia linked to PEG. To accurately measure plasma, asparagine is not mostly feasible outside the clinical trial context. The optimal therapeutic level where plasma Asparagine is fully depleted, but the measurement of its plasma values faces uncertainty due to technical issues that call the validity into question. There is still room for improvement even though asparaginase is a well-established cornerstone of ALL/LBL therapy. Some approaches, like encapsulating L-asparaginase in donor-derived erythrocytes, appear promising for overcoming potential hypersensitivity. When the cleaved asparagine enters the erythrocyte, it does so while the drug is hidden from the patient's immune system. However, on observing the current available data, the information regarding the asparaginase levels and their PK value is needed in a larger group so that asparaginase dose regimens can be optimized. A more direct evaluation of the SAA levels required for the best outcomes might be made in future studies by correlating SAA values with outcomes in sizable uniformly treated cohorts.[3]

Conclusions

Pegaspargase is more tolerable, less immunogenic, and equally effective when compared with native L-asparaginase. If at all possible, all patients with childhood leukemia should have their levels of SAA, an indicator of the enzyme's capacity

to deplete asparaginase, If at all possible, all patients with childhood leukemia should have their levels of SAA, an indicator of the enzyme's capacity to deplete asparaginase monitored. Biosimilar pegaspargase maintained good SAA levels at 7 and 14 days after infusion. However, further evaluation should be considered regarding therapeutic SAA levels and its correlation with complete plasma depletion of asparagine (including CSF values). Since it has been found that pegaspargase has a prolonged effect, is convenient to administer, and has a good safety profile, it can be recommended to replace native asparaginase. However, larger studies are warranted for exploring further scope.

Note

The abstract of this text was published in the Supplementary issue: Abstracts of the 25th Annual Conference of the Pediatric Hematology Oncology chapter of the Indian Academy of Pediatrics (PHOCON 2022), N Delhi in November 2022 with doi: 10.1016/j.phoj.2022.10.176

The manuscript has been read and approved by all the authors, that the requirements for authorship (Pg. 18) have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form.

Patient Consent

None declared.

Ethics Approval

This study was approved by Institutional Ethics Committee at Kasturba Hospital, Manipal and the procedures used in this study adhere to the tenets of the Declaration of Helsinki.

All procedures performed in studies involving human participants were in accordance with the ethical standards and by approval from the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee (DHR Registration No. EC/NEW/INST/2019/374, Dated 14th April 2021, IEC: 356/2021) and was registered at CTRI- REF/2021/08/046121. It was performed in line with the latest Helsinki Declaration's guiding principles from 2013.

Authors' Contributions

Vasudeva Bhat K conceptualized and designed the study. Archana M.V., Arjun Asok, and Krishnananda Prabhu helped in data acquisition and manuscript preparation.

Source of Funding

None declared.

Conflicts of interest/Competing Interest

None declared.

Acknowledgment

None declared.

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The Role of Reticulocyte Hemoglobin Content in Diagnosing Iron Deficiency in Childhood Cancer

Murti Andriastuti[1] Anisa Dwi Fathinasari[2] Afifa Fahriyani[1] Kanthi Soraca Widiatmika[2] Khansa Salsabila[2] Fitri Primacakti[1]

[1] Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[2] Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Ind J Med Paediatr Oncol 2024;45:396–401.

Address for correspondence Murti Andriastuti, Sp.A(K), Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Pangeran Diponegoro No. 71, Kenari, Senen, Central Jakarta 10430, DKI Jakarta, Indonesia (e-mail: murtiandri@yahoo.com).

Abstract

Background The prevalence of iron deficiency (ID) and iron deficiency anemia (IDA) in children with cancer is not well studied. The detection of ID and IDA using sensitive laboratory tools may facilitate early diagnosis and treatment in this cohort. In this regard, reticulocyte hemoglobin (Ret-He) content serves as a cost-effective measurement that remains unaffected by inflammation, unlike the ferritin test.

Aim The objective of this study is to analyze the role of Ret-He as a diagnostic tool to identify functional and absolute ID and IDA in children with cancer.

Methods We conducted a cross-sectional study in children aged 0 to 18 years. Blood samples were collected to compare Ret-He values with iron status, reflected by hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), serum iron (SI), total iron binding capacity (TIBC), and ferritin and transferrin saturation. The overall discriminative power of Ret-He in detecting ID and IDA was assessed using receiver operating characteristic analysis.

Results Of the 135 children included in the study, 58 (43.0%) had anemia. Among them, 20 (14.8%) had IDA (8 [5.9%] absolute and 12 [8.9%] functional), while 25 (18.5%) had ID (16 [11.9%] absolute and 9 [6.7%] functional). The Ret-He value was significantly related to iron status ($p \leq 0.002$). Ret-He was also shown to have a significant correlation with the abovementioned hematological parameters ($p = 0.000$), except TIBC. Multivariate analysis revealed a significant relationship between Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$) and Ret-He. Ret-He values of 33.7, 32.7, 32.4 and 28.6 pg were established as optimal cut-off values to identify functional ID, absolute ID, functional IDA, and absolute IDA, respectively.

Conclusion Ret-He is a reliable diagnostic tool for absolute and functional IDA in children with cancer.

Keywords
- absolute ID
- absolute IDA
- childhood cancer
- functional ID
- functional IDA
- hemoglobin
- Ret-He

Introduction

Children suffering from chronic diseases, such as cancer, are more susceptible to both iron deficiency (ID) and iron deficiency anemia (IDA). A study conducted by the European Cancer Anemia Survey (ECAS) revealed that 39% of children with cancer were anemic at the study's onset. This value increased to 67% after chemotherapy. Moreover, 42% were identified as iron deficient.[1,2]

article published online
March 21, 2024

DOI https://doi.org/10.1055/s-0044-1779047.
ISSN 0971-5851.

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

Anemia in cancer patients can arise from factors like malnutrition, malabsorption, chronic inflammation, bleeding, therapy-induced myelosuppression, bone marrow infiltration, hemolysis, hypersplenism, and ID. The disrupted iron homeostasis and metabolism in cancer patients are primarily due to chronic inflammation, which leads to iron sequestration in macrophages, causing limited iron availability for red blood cell production in the bone marrow.[3,4]

IDA can adversely affect physical performance, leading to general weakness and fatigue and potentially reducing the effectiveness of chemotherapy/radiotherapy against tumors.[3] Thus, the early detection of ID is crucial to address it with simple treatments like iron supplementation or erythropoietin and limit the need for packed red cell transfusion in cancer patients.

Although the gold-standard diagnostic tool for ID is bone marrow staining with Prussian blue, this method is invasive and expensive.[5] In 2010, the American Academy of Pediatrics (AAP) stated that ID can be diagnosed by evaluating ferritin and c-reactive protein levels or measuring reticulocyte hemoglobin (Ret-He), with low hemoglobin levels indicating IDA.[6] However, ferritin is an acute-phase protein that can increase under inflammatory conditions, including malignancy. The European Society for Medical Oncology (ESMO) guidelines define ID in cancer patients as ferritin levels <100 ng/mL or transferrin saturation (TS) $< 20\%$.[3,5]

In recent years, the potential of Ret-He content as an early marker for ID has been highlighted. Reticulocytes are immature erythrocytes released from the bone marrow that can reflect the erythropoiesis status over the preceding 3 to 4 days.[7,8] Unlike ferritin, Ret-He is not influenced by inflammation as it is not an acute-phase protein.[6,9] The hemoglobin content in reticulocytes can be assessed through measures such as Ret-He content (CHr or Ret-He), both utilizing flow cytometry and reported in picograms.[8,10,11] The Ret-He laboratory test can be performed alongside routine blood tests without the need for additional blood samples.[9,12]

Research to determine the optimal Ret-He cut-off values for ID and IDA in pediatrics, particularly pediatric cancer patients is ongoing.[12–14] In this study, we investigated the diagnostic value of Ret-He in identifying ID and IDA in children with cancer to facilitate the simple detection of these conditions.

Materials and Methods

Subjects

A cross-sectional study was conducted in Cipto Mangunkusumo Hospital from March to June 2021. Hospitalized and outpatient children aged 0 to 18 years with cancer were selected as participants. Patients with a history of iron therapy or blood transfusion in the past month were excluded. Written consent and assent were obtained from the subjects' parents or legal guardians and adolescent patients.

Inclusion and Exclusion Criteria

The inclusion criteria for this study comprised children between the ages of 0 and 18 years with cancer who were either hospitalized or received outpatient treatment. Patients who received iron therapy or blood transfusion within the past month were excluded. No oral iron therapy was initiated for IDA patients.

Laboratory Methods

Venous blood samples (6 mL) were obtained from the subjects. Iron parameters, including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte hemoglobin (Ret-He), ferritin, serum iron (SI), and total iron binding capacity (TIBC), were measured via standard techniques. TS was calculated using the formula SI/TIBC $\times$ 100. All parameters were analyzed in the Clinical Pathology Laboratory of Cipto Mangunkusumo Hospital.

Iron Status Definition

The World Health Organization defines anemia as a low Hb value according to age: Hb <11 g/dL in children aged 6 to 59 months, <11.5 in 5 to 11-year-olds, <12 g/dL in 12 to 14-year-olds, <12 g/dL in unpregnant girls aged ≥ 15 years, and <13 g/dL in boys aged ≥ 15 years.[15] In this study, ESMO criteria were used to evaluate iron status in children: (1) absolute IDA with low Hb and ferritin <100 ng/mL, (2) functional IDA with low Hb and TS $<20\%$ and normal ferritin ≥ 100 ng/mL, (3) absolute ID with normal Hb and ferritin <100 ng/mL, and (4) functional ID with normal Hb and TS $<20\%$ and ferritin ≥ 100 ng/mL.[16]

Primary and Secondary Outcomes

The primary outcome of this study was the establishment of optimal Ret-He cut-off values for different types of absolute and functional ID or IDA, with their respective sensitivities, specificities, and predictive values. The secondary outcome was the evaluation of iron status in children with cancer, including the prevalence of ID and IDA. Laboratory indices, such as Hb, MCV, MCH, MCHC, SI, ferritin and TS, and their relationship with Ret-He, were also analyzed.

Statistical Analysis

The correlation between iron status and Ret-He was determined with analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on the data distribution. Normality was assessed using the Kolmogorov–Smirnoff test. ANOVA with Tukey's post-hoc analysis was performed. Ret-He was also compared with other laboratory parameters through correlation analysis using the Pearson and nonparametric Spearman methods. Significant variables were subsequently subjected to multivariate analysis using linear regression. The overall discriminative power of Ret-He to detect iron depletion, ID, and IDA was assessed using receiver operating characteristic (ROC) analysis. Cut-off values were determined for each iron status using Youden's index, where (sensitivity + specificity) –1 had the highest value. A p-value of <0.05 was considered statistically significant.

Ethics

The Ethics Committee of the Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, approved this study (No. KET-1010/UN2.F1/ETIK/PPM.00.02/2020) on September 14, 2020. This study did not involve any animals. All the research methods involving humans were performed according to the ethical guidelines established by the responsible committee overseeing human experimentation at the institutional and national levels. They also complied with the 1975 Helsinki Declaration, updated in 2013.

Results

A total of 146 children were initially included in this study. Eleven subjects had incomplete data and were excluded; thus, the final study population comprised 135 children (►**Supp. Fig. 1**). The characteristics of these subjects are shown in ►**Table 1**.

Iron Status in Children with Cancer

In this study, 58 children (43.0%) had anemia. The prevalence of IDA was 14.8% (20/135), while anemia in the remaining subjects had other causes. Absolute IDA was found in 8 subjects and functional IDA in 12 subjects. The prevalence of ID was 18.5% (25/135). Absolute ID was found in 16 subjects and functional ID in 9 subjects. Analysis of laboratory indices showed that Hb, MCH, MCHC, Ret-He, SI, and TS were statistically significantly related to iron status. All the laboratory parameters assessing iron status in the abovementioned subgroups were statistically significant except ferritin, MCV, and TIBC (►**Table 2**).

Diagnostic Performance of Ret-He

The diagnostic performance of Ret-He is shown in ►**Supp. Fig. 2**. The ROC curve revealed Ret-He as a reliable diagnostic tool for functional ID, absolute ID, functional IDA, and absolute IDA, with area under the curves (AUCs) of 72.4% ($p = 0.033$, 95% confidence interval [CI]: 0.54–0.91), 77.8% ($p = 0.001$, 95% CI: 0.65–0.91), 69.7% ($p = 0.034$, 95% CI: 0.50–0.89), and 73.1% ($p = 0.037$, 95% CI: 0.50–0.97), respectively. From the correlation analysis, Ret-He was found to be positively related to transferrin (0.54) and ferritin (0.44), as well as the remaining hematological parameters except for TIBC (►**Table 3**). We also conducted a multivariate analysis to examine the relationship between other hematological parameters and Ret-He. A significant relationship was observed between Ret-He and Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$); see ►**Table 4**. By assessing Youden's index, we determined the optimal cut-off values of Ret-He with their respective sensitivities and specificities for each group (►**Table 5**). The optimal cut-off values for functional ID, absolute ID, functional IDA, and absolute IDA were 33.7, 32.7, 32.4 and 28.6 pg, respectively. On the contrary, the cut-off values with the highest specificity for the aforementioned groups were 28.4–30.25, 27.85–30.25, 27.85–30.25, and 27.25–30.25 pg, respectively.

Table 1 Characteristics of subjects

Characteristics	Frequency (*n*)	Percentage (%)
Gender		
Male	75	55.6
Female	60	44.4
Age (years), mean ± SD, median (IQR)	8.4 ± 4.7	7 (8)
Cancer type		
ALL	74	54.8
AML	7	5.2
CML	9	6.7
Lymphoma	6	4.4
Solid cancer	39	28.9

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; IQR, interquartile range; SD, standard deviation.

Discussion

The prevalence of anemia in our pediatric cancer study was 43.0%, comparable to a study by ECAS (39%).[1] In this study, the overall prevalence of IDA was 14.8%, similar to prior studies in healthy school-aged children in Jakarta (13[12] and 14%[17]). Notably, no previous study has examined the prevalence of anemia and ID in children with cancer in Indonesia.

In cancer patients, iron metabolism and regulation are altered due to chronic disease, chronic blood loss, nutritional deficiency, increased consumption by cancer cells, myelosuppressive chemotherapy, and metastases. ID can contribute to DNA damage, genomic instability, and immunological dysfunction during cancer development.[18] The timely diagnosis and treatment of ID are crucial in cancer patients to prevent complications associated with anemia, such as impaired exercise capacity, fatigue, reduced quality of life, and an overall poor prognosis.[4,7,18] While functional ID is typically predominant,[4,16,18–20] absolute ID was more prevalent in this study, indicating reduced iron stores as the main cause. Thus, restoring iron stores through appropriate therapies is essential.

Iron status assessment in cancer patients remains challenging due to the lack of a gold standard and the impact of inflammatory conditions on standard biochemical tests such as SI and ferritin. According to the AAP, Ret-He is the strongest predictor for ID in children.[6] It remains stable compared with other markers and is unaffected by conditions like infection, inflammation, and malignancy.[6,7,21] In our study, Ret-He showed a significant positive correlation with other hematological parameters ($p = 0.000$) except for TIBC. Multivariate analysis revealed a significant relationship between Ret-He and Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$). The simultaneous analysis of all laboratory parameters in multivariate analysis allows for assessing the effects of variables, as each laboratory parameter represents a specific definition of ID.

Unfortunately, there is no universal cut-off value or guidelines for Ret-He in diagnosing ID or IDA. Prior studies have

Table 2 Comparison of iron status

	Normal ($n = 52$)	Functional ID ($n = 9$)	Absolute ID ($n = 16$)	Functional IDA ($n = 12$)	Absolute IDA ($n = 8$)	*p*-Value
Hb	13.00 ± 0.96	12.33 ± 0.86	12.58 ± 1.45	10.09 ± 1.16	10.44 ± 1.37	<0.001
MCV	85.48 (75–96)	80.39 (75–87)	77.43 (60–85)	84.03 (78–97)	80.05 (71–85)	0.000
MCH	29.85 (25–34)	27.80 (25–30)	27.40 (19–30)	27.90 (26–33)	27.60 (20–29)	<0.001
MCHC	34.75 ± 1.30	34.29 ± 0.93	34.05 ± 1.28	33.93 ± 1.17	32.64 ± 2.19	0.001
Ret-He	34 (26–38)	32.5 (27–36)	31.2 (20–35)	31.50 (17–36)	30 (19–36)	<0.002[a]
Ferritin	709.55 (113–96,773)	191.03 (111–5,039)	38.35 (11–95)	716.79 (187–3,483)	14.68 (1–81)	0.79
SI	93.5 (40–291)	39 (9–54)	73.5 (24–132)	29.5 (10–52)	45 (19–82)	<0.001[a]
TS	40 (21–92)	17 (9–18)	23 (10–40)	15 (5–20)	14.5 (6–26)	<0.001[a]
TIBC	238 (101–258,000)	231 (103–326)	315 (247–389)	214.5 (168–310)	330 (193–382)	0.93

Abbreviations: ANOVA, analysis of variance; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity; TS, transferrin saturation.
Note: Data are presented as mean ± standard deviation or median (min–max).
[a]Kruskal–Wallis for nonparametric analysis as alternative to ANOVA test.

Table 3 Correlation analysis between Ret-He and hematological parameters

Parameters	Correlation coefficient	Sig. (2-tailed)
Hb[a]	0.431	0.000
MCV	0.474	0.000
MCH	0.627	0.000
MCHC[a]	0.668	0.000
SI	0.489	0.000
TIBC	−0.76	0.460
Transferrin	0.540	0.000
Ferritin	0.443	0.000

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity.
Note: Remaining data are analyzed with nonparametric Spearman.
[a]Data are analyzed using Pearson correlation.

Table 4 Multivariate logistic regression analysis between Ret-He and hematological parameters

		Unstandardized coefficients		Standardized coefficients	*t*	Sig.
		B	Standard error	Beta		
Ret-He	Hb	0.392	0.198	0.154	1.983	0.051
	MCV	0.009	0.030	0.025	0.313	0.755
	MCH	0.642	0.166	0.427	3.878	0.000
	MCHC	0.841	0.243	0.315	3.466	0.001
	SI	0.007	0.11	0.101	0.599	0.551
	TIBC	−7.131E − 007	0.000	−0.005	−0.072	0.943
	Transferrin	−0.006	0.028	−0.040	−0.231	0.818
	Ferritin	−1.703E − 005	0.000	−0.043	−0.637	0.526

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity.

Table 5 Ret-He cut-off to evaluate iron status

Parameter	AUC	Cut-off	Sensitivity	Specificity	*p*-Value
Functional ID					
	72.4%	33.7[a]	88.9	55.8	0.033 (0.54 – 0.91)
		33.65 – 34.65	88.9	32.7 – 55.8	
		28.4 – 30.25	22 – 33	90.4 – 98.1	
Absolute ID					
	77.8%	32.7[a]	81.3	73.1	0.001 (0.65 – 0.91)
		33.4 – 34.05	81.3 – 87.5	44.2 – 57.7	
		27.85 – 30.25	31.3 – 37.5	90.4 – 98.1	
Functional IDA					
	69.7%	32.4[a]	66.7	75.0	0.034 (0.50 – 0.89)
		34.55 – 35.25	83.3	21.2 – 36.5	
		27.85 – 30.25	25 – 41.7	90.4 – 98.1	
Absolute IDA					
	73.1%	28.6[a]	50.0	98.1	0.037 (0.50 – 0.97)
		35 – 35.25	87.5	21.2 – 26.9	
		27.25 – 30.25	37.5 – 50	90.4 – 98.1	

Abbreviations: AUC, area under the curve; ID, iron deficiency; IDA, iron deficiency anemia,
[a]Optimal cut-off based on the highest Youden index.

suggested various cut-offs, ranging from 25 to 29 pg,[22–24] with sensitivities between 70 and 94% and specificities from 72 to 80% in healthy children. Population studies in healthy Indonesian children aged 6 to 18 years and 6 to 12 years found cut-offs of 27.8[12] and 27.8 pg,[14] respectively. In cancer patients, one study in adolescents and adults aged 11 to 94 years reported a higher Ret-He cut-off of 32.0 pg for ID.[7] In our study, cut-offs for functional ID, absolute ID, functional IDA, and absolute IDA were 33.7, 32.7, 32.4, and 28.6 pg, respectively. Studies in children on hemodialysis reported cut-off values of 28.9[25] and 29.0 pg.[26] Both these values are more similar to the cut-offs in healthy children. Besides determining the optimal fixed values to evaluate iron status, we also analyzed a range of cut-offs for clinical utility. We found that higher cut-offs (33.4–35.25 pg) are suitable for screening purposes, while lower values (27.25–30.25 pg) are more appropriate for diagnosis.

Ret-He proved to be a reliable diagnostic tool for functional ID, absolute ID, functional IDA, and absolute IDA, with respective AUCs of 72.4, 77.8, 69.7, and 73.1%. It exhibited the highest diagnostic performance in the absolute ID group, demonstrating high sensitivity and specificity. In the functional ID and absolute ID groups, sensitivity was higher than specificity, indicating its reliability as a screening tool. In the functional and absolute IDA groups, specificity was higher, making Ret-He a reliable diagnostic tool supported by a good negative predictive value. Ret-He has been reported as superior in diagnosing ID in children by Brugnara et al,[23] Andriastuti et al,[12] and Syed et al.[27] Using Ret-He as a diagnostic tool can reduce the need for additional iron studies, improving cost-effectiveness and patient comfort.[28,29]

Our study has limitations that could potentially introduce bias, such as the restriction of the population to subjects who had not received blood transfusions within the past month and the lack of assessment of transfusion frequency and volume. However, from a clinical perspective, the test can effectively be used as a diagnostic tool either at baseline or for new cases, considering the high prevalence of IDA. This study is the first to report the prevalence of ID and IDA in Indonesian children with cancer. Additionally, it is the first to compare Ret-He to other laboratory parameters as a diagnostic tool for pediatric cancer in Indonesia. Further cohort studies are needed to evaluate Ret-He after iron therapy and explore its impact on anemic and iron-deficient children with cancer, including newly diagnosed patients.

Conclusion

The prevalence of IDA and ID in childhood cancer in this study was 14.8 and 18.5%, respectively. Ret-He emerged as a reliable diagnostic tool, showing a significant positive correlation with other hematological parameters. Given the burden of IDA in children, it is important to understand its impact on children diagnosed with cancer. The relationship between IDA and cancer in this context is currently understudied and requires further exploration. The present study provides valuable insights into iron metabolism in cancer. It also supports the existing evidence that Ret-He remains unaffected by inflammation in cancer. However, further research is needed to determine the clinical utility of these tests in this population.

Patient Consent

Patient consent was obtained from every subject.

Funding
This study was supported by the International Indexed Publication (Publikasi Terindeks Internasional or PUTI) Universitas Indonesia research grant.

Conflicts of Interest
None declared.

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Acute Appendicitis in Children with Hematological Malignancies: The Need for Early Diagnosis and Prompt Treatment—A Single-Center Case Series

Shruti Kakkar[1] Arihant Jain[2] Evani Jain[3] Anubhavv Gupta[4] Navneet Kaur[1] Anirudh Jain[3] Alka Grewal[2] Sushil Budhiraja[2] Chandan Kakkar[5]

[1] Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana, Punjab, India
[2] Department of Pediatric Surgery, Dayanand Medical College and Hospital, Ludhiana, Punjab, India
[3] MBBS, Dayanand Medical College and Hospital, Ludhiana, Punjab, India
[4] Department of Surgery, Dayanand Medical College and Hospital, Ludhiana, Punjab, India
[5] Department of Radiodiagnosis, Dayanand Medical College and Hospital, Ludhiana, Punjab, India

Address for correspondence Shruti Kakkar, MBBS, MD, Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana 141001, Punjab, India (e-mail: drahujashruti@gmail.com).

Ind J Med Paediatr Oncol 2024;45:402–409.

Abstract

Introduction Appendicitis in patients with hematological malignancies presents with vague symptoms, thus requiring a high degree of suspicion for early diagnosis and treatment to prevent complications.

Objectives The aim of this article was to describe the demographic, clinicoradiological, operative findings, and outcomes in patients with acute appendicitis with underlying hematological malignancies.

Materials and Methods A retrospective review of pediatric patients with hematological malignancy who developed acute appendicitis was conducted. Medical records of patients were reviewed for patient demographics, disease status, signs, and symptoms at the time of diagnosis of acute appendicitis, and outcome. The laboratory, radiological, and histological findings were retrieved from the hospital records.

Results Six (2.4%) patients developed acute appendicitis over the past 8 years among a total of 254 patients treated for hematological malignancies in the unit. Five patients had underlying acute lymphoblastic leukemia (ALL) and one had acute myeloid leukemia (AML). Of the five patients, three were in postremission consolidation, one each in the delayed intensification and maintenance phase of chemotherapy. The child with AML was on induction chemotherapy for the first relapse at the time of diagnosis. Fever and abdominal pain were the common presenting symptoms. Diagnosis was made on ultrasound abdomen in five patients, and one patient was diagnosed on computed tomography. All patients underwent open appendectomy. Two patients had evidence of appendiceal perforation. Three patients had neutropenia at the time of developing appendicitis and underwent appendectomy regardless of the absolute neutrophil count (ANC). Five patients recovered well, and chemotherapy was restarted within 2 weeks of appendectomy. One

Keywords
- acute appendicitis
- hematological malignancies
- neutropenia

article published online
May 24, 2024

DOI https://doi.org/10.1055/s-0044-1786679.
ISSN 0971-5851.

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

patient developed a superficial surgical site infection. and one patient with relapsed AML expired due to refractory septic shock.

Conclusion Acute appendicitis in patients with hematological malignancies can present with subtle signs and symptoms. Appendectomy can be safely performed irrespective of the ANC.

Introduction

The gastrointestinal tract is one of the most common sources of infective complications in children with hematological malignancies, with a specific predilection to the ileocecal region. Acute appendicitis is the most common surgical emergency in children with a lifetime cumulative incidence rate of 9% in the general population. Younger children are at an increased risk of complicated appendicitis.[1,2] The reported incidence of appendicitis is as low as 0.5% in children with leukemia and most children present with vague abdominal signs requiring a high index of suspicion for early diagnosis and treatment. The presence of neutropenia and/or thrombocytopenia, along with underlying disease conditions, has led to controversy over whether to opt for medical or surgical management in these patients.[3,4] Here we present the data of six children with underlying hematological malignancy managed for acute appendicitis at our center.

Materials and Methods

Study Design

A retrospective observational study was conducted in the Pediatric Hematology Oncology unit of the Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana.

Sample Size

All pediatric patients undergoing treatment for a hematological malignancy who developed acute appendicitis from August 2014 to December 2022 were included in the study. The data regarding the patient's age, gender, anthropometry, underlying disease status, signs and symptoms, laboratory, radiological, and histopathological data, treatment modalities, and outcomes at the time of development of acute appendicitis were retrieved from the hospital records. The diagnosis of acute appendicitis was made radiologically on an ultrasound (US) or computed tomography (CT) scan in the presence of blind-ending incompressible tubular structure in the right lower quadrant with an overall diameter of more than 6 mm and raised echogenicity of surrounding mesenteric fat.[5] It may or may not be associated with free fluid or abscess in the abdominal cavity.

The patients with ALL are treated as ALL-BFM 1995 protocol and patients with acute myeloid leukemia (AML) receive one to two courses of $(7+3)$ induction followed by three courses of high-dose cytarabine.[6,7]

Inclusion and Exclusion Criteria

All patients less than 18 years of age who developed acute appendicitis while on treatment for an underlying hematological malignancy were included in the study. Non-availability of data/incomplete data regarding any of the studied variables was considered an exclusion criterion.

Primary and Secondary Outcomes

Primary Outcome

Outcome of patients with hematological malignancies who developed acute appendicitis.

Secondary

A) To describe clinical, laboratory, and radiological findings.
B) To describe the operative findings.
C) The time taken to start oral feed/duration of hospital stay.
D) The time taken to reinitiate chemotherapy.

Statistical Analysis

The data collected was tabulated in Excel sheets and statistical analysis was performed using descriptive methods. Data were described in terms of range; mean $\pm$ standard deviation ($\pm$standard deviation), frequencies (number of cases), and relative frequencies (percentages) as appropriate.

Results

Over a period of 8 years, 254 children were treated for hematological malignancies and six of them developed acute appendicitis (2.4%) during the treatment. Among the six patients diagnosed with appendicitis, five had an underlying diagnosis of ALL, and only one had AML. The median age at the time of diagnosis of appendicitis was 7.5 years (range: 4–15 years). All patients were male. Of the five ALL patients, three were in the postremission consolidation phase, one was in the delayed intensification phase, and one patient was on maintenance chemotherapy. The sixth patient with AML was on induction chemotherapy for the first relapse (►**Table 1**).

Three patients had neutropenia at the time of surgery, with absolute neutrophil count (ANC) being as low as 10 cells/µL in the patient with relapsed AML. The median ANC at the time of admission and surgery was 847.5 cells/µL (range: 10–7,040 cells/µL) and 1,299.5 cells/µL (range: 10–7,921 cells/µL), respectively. The median hemoglobin and median platelet count at the time of surgery were 9 g/dL and 133,500 cells/µL, respectively with thrombocytopenia in two patients.

All patients had a fever, five had abdominal pain, and four patients had classical tenderness at the right lower quadrant

Indian Journal of Medical and Paediatric Oncology Vol. 45 No. 5/2024 © 2024. The Author(s).

Table 1 Demographic details, duration of symptoms, and laboratory findings of leukemic children with acute appendicitis

Patient no.	1	2	3	4	5	6
Age in years	9	4	15	7	8	7
Gender	Male	Male	Male	Male	Male	Male
Weight (kg) and Z score as per CDC weight for age.	25 (−0.9)	17 (0.34)	30 (−4.33)	23 (−0.05)	25 (−0.19)	19.7 (−1.22)
Height (cm) and Z score as per CDC height for age.	128 (−0.9)	107 (1.1)	157 (−1.6)	121 (−0.2)	125 (−0.5)	115 (−1.3)
Diagnosis	Pre-B ALL	Pre-B ALL	Pre-B ALL	Pre-B ALL	Pre-B ALL	Relapsed AML
Disease status	Remission	Remission	Remission	Remission	Remission	Relapse
Phase of treatment	Delayed intensification	Consolidation	Consolidation	Consolidation	Maintenance	Reinduction
Duration of symptoms before surgery (days)	2	2	2	18	7	7
ANC at admission (cells/μL)	1,278	1,239	456	7,040	140	10
ANC at surgery(cells/μL)	4,268	2,059	540	7,921	480	10
Platelet count at admission (cells/μL)	4,00,000	1,10,000	2,04,000	3,21,000	15,000	15,000
Platelet count at surgery (cells/μL)	1,17,000	2,28,000	1,50,000	7,19,000	31,000	11,000
Hemoglobin at admission (g/dL)	11.6	8.6	7.6	9.7	8.2	8.7
Hemoglobin at surgery (g/dL)	7.9	8.7	9.3	8.1	9.6	9.7

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil counts; CDC, Centers for Disease Control and Prevention.

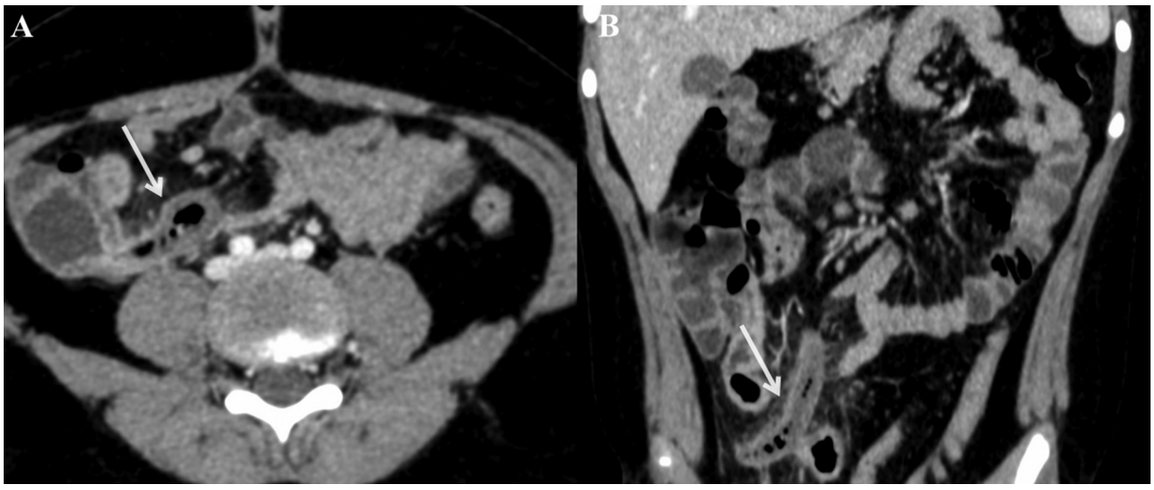

Fig. 1 (A, B) Axial and coronal postcontrast images showing a dilated appendix (arrow) in the right iliac fossa with significant peri-appendiceal fat stranding in keeping with acute appendicitis.

of the abdomen. Three patients were diagnosed with acute appendicitis within 24 hours of the onset of signs and symptoms and underwent emergency appendectomy after stabilization. Two patients had a delay in diagnosis due to the absence of signs of tenderness in the right lower quadrant and one of them required a CT scan (►**Fig. 1**) to establish the diagnosis preoperatively. Another patient was being managed for febrile neutropenia and did not have any localizing signs. An US abdomen done to determine the focus for persistent fever revealed peri-appendicular echogenic collection. The collection was drained by US-guided percutaneous technique, and an interval appendectomy was performed 2 weeks later. At the time of admission, all patients were started on broad-spectrum antibiotics (cefoperazone/sulbactam and amikacin) as per febrile neutropenia protocol. Oral feeds were withheld once diagnosed with appendicitis and patients were administered maintenance intravenous fluids. Paracetamol was used for the management of pain in all patients. All children underwent open appendectomy. The antibiotics were modified in the patient who underwent percutaneous drainage based upon the pus culture and sensitivity pattern. The pus culture showed growth of *Klebsiella pneumoniae* sensitive to carbapenems. Four patients required transfusion of blood components perioperatively. Two patients had developed complicated appendicitis in the form of appendicular perforation. One patient developed a superficial surgical site infection that was managed by regular bedside wound care. One of the patients had a coexistent coronavirus 2019 infection at the time of diagnosis of appendicitis but did not affect the surgical intervention or outcome.

Five patients recovered well and were started on an oral diet at a mean duration of 35 hours after surgery (range: 24–48 hours). Chemotherapy was restarted after a mean duration of 11.2 days (4–17 days) from the onset of symptoms. Patients were discharged after a mean postoperative stay of 7 days (range: 5–10 days). One patient had a delay in diagnosis due to inconclusive US findings. The patient had persistent fever with neutropenia on day 4 of admission; hence, antibiotics were upgraded, and antifungal therapy was added empirically as per the institutional policy. A CT scan conducted on day 5 due to clinical worsening and development of abdominal distension revealed the presence of appendicular perforation, which necessitated surgical intervention. The patient developed features of septic shock on postoperative day 4 requiring inotropic (norepinephrine and dobutamine infusion) support and died on postoperative day 8 due to refractory septic shock (►**Table 2**). All six patients had histology-proven appendicitis with no specimen showing leukemic infiltration on hematoxylin-eosin staining and immunohistochemistry (►**Fig. 2**).

Discussion

Acute appendicitis is a rare gastrointestinal complication in children being treated for hematological cancers. The reported incidence of acute appendicitis in children with hematological malignancy is 0.5 to 4.5% as shown in multiple studies (►**Table 3**).[8–10] This study revealed an incidence rate of 2.4% among these children (►**Table 3**). There are multiple causes of the acute surgical abdomen in children undergoing treatment for leukemia but the most common are acute appendicitis and typhlitis.[9] Typhlitis is characterized by the cecal or terminal ileal wall thickness of more than 3 mm on US for a variable length of the bowel segment. Mucosal injuries from chemotherapy, bacterial overgrowth, and neutropenia contribute to typhlitis.[11] The most probable etiology of appendicitis in children with leukemia is luminal obstruction by a fecolith, which is similar to patients with appendicitis in the general population. Other causes of appendicitis may include lymphoid hyperplasia secondary to a viral infection, enterocolitis in a neutropenic patient, or

Table 2 Image findings, operative,[a] and pathological findings with postoperative details and outcomes

Patient no.	Radiological findings	Operative findings	HPE findings	Time taken to initiate oral soft diet (days)	Time taken to restart chemotherapy (days)	Postoperative hospital stay (days)	Outcome	Perioperative complications
1	Dilated inflamed appendix (caliber 7 mm)	Retrocecal inflamed appendix	Acute appendicitis	1	17	4	Recovered	None
2	Inflamed edematous appendix (12 mm) Raised peri-appendiceal echogenicity	Retrocecal inflamed appendix	Acute appendicitis	1	10	6	Recovered	None
3	Inflamed edematous appendix (6.7 mm) Raised peri-appendiceal echogenicity (subhepatic location)	Retrocecal inflamed appendix with the tip in subhepatic region	Acute appendicitis	2	14	6	Recovered	Superficial surgical site
4	Dilated appendix with peri-appendiceal collection (4.7×6.6 cm)[b]	Retrocecal appendix with sloughed-off tip Densely adherent omentum in right iliac fossa & pelvis	Acute suppurative appendicitis	2	10	10	Recovered	None
5	Inflamed edematous appendix (10 mm) raised peri-appendiceal echogenicity	5 cm long appendix, retrocecal in location Distal ⅔ inflamed and edematous	Acute appendicitis	1	7	5	Recovered	None
6	No signs of inflammation on US[c]	Inflamed retrocecal appendix wrapped in the omentum Inflamed ileocecal junction	Acute gangrenous appendicitis	Not started	Not started	8	Expired	Septic shock

Abbreviations: CECT, contrast-enhanced computed tomography; HPE, histopathological examination.
[a]All patients underwent open appendicectomy.
[b]Ultrasound-guided drainage of purulent contents.
[c]Findings on CECT abdomen: Inflamed appendix with a maximum diameter of over 6mm.

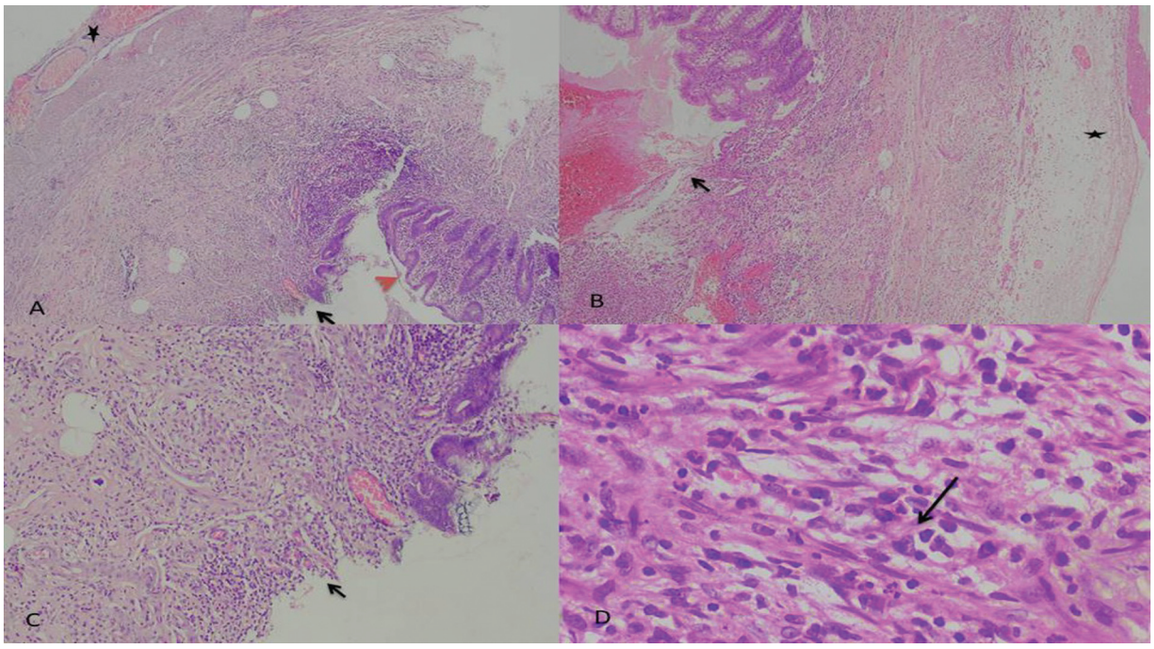

Fig. 2 Histopathological examination of the surgical specimen. (**A**, **B**) Scanner view showing mucosal ulceration (black arrow) with transmural infiltration by neutrophils along with serosal congestion in two different areas shown with normal mucosa (orange arrowhead; hematoxylin and eosin [H&E] 40X). (**C**) Low power view showing ulceration of mucosa (black arrow; H&E 100X). (**D**) High-power view showing the presence of neutrophils (black arrow) in muscularis propria of appendix (H&E 400X).

leukemic infiltration of the appendix. The incidence of leukemic infiltration of the appendix is negligible as shown by others; none of the patients had leukemic infiltration of appendix in our cohort (►**Table 3**).[12–14] It is difficult to diagnose appendicitis in immune-compromised patients with leukemia due to the absence of typical signs and symptoms.[8,9,15] Timely diagnosis of appendicitis is key to improving overall survival in these children.[16] Several studies have confirmed that US and contrast-enhanced CT aid in establishing the diagnosis for this group of children as highlighted in ►**Table 3**.[4,9,17,18] In our cohort, US successfully diagnosed appendicitis in all patients except for one, who later underwent a CT scan for confirmation.

A debate continues between surgical and nonsurgical approaches to treat appendicitis in leukemic children. Appendectomy has been the mainstay of management of acute appendicitis in the past. There is emerging data that nonoperative management with broad-spectrum antibiotics may be equally effective and safe for the management of uncomplicated acute appendicitis. The complications of early surgery may include blood loss, bowel obstruction, injury to bowel wall or surrounding tissues, abscess/fistula formation, dissemination of infection, and wound complications. The management of complicated acute appendicitis, that is, presence of perforation or abscess formation, remains controversial.[1,2]

Many studies till the late 1970s showed that patients managed medically had poor outcomes.[19] Exelby et al and Ver Steeg et al advocated early surgical intervention that improved survival by 50% in these children.[20,21] The distorted anatomy of inflamed tissues in delayed surgical interventions raises concerns about a higher risk of perioperative complications. Delaying surgical resection may also increase the risk of progression and recurrence of complicated appendicitis.[22] Park et al recommended a non-surgical approach in the initial stages till the ANC improves.[5] Patients with persistent symptoms after an increase in ANC or sudden worsening were recommended surgery. Neutropenic children with acute appendicitis should be treated medically without surgery, according to Wiegering et al.[4] All five children recovered well in their study, and none developed recurrent appendicitis. In our institute, all children independent of the ANC at the time of diagnosis undergo early appendectomy, which reduces the recovery time postoperatively. At the time of surgery, three of our patients had moderate-to-severe neutropenia, reinforcing the feasibility of appendectomy in neutropenic patients. Mortellaro et al demonstrated that an early appendectomy (within 24 hours of the onset of symptoms) is safe in neutropenic patients and did not result in an increased risk of infections or mortality during the perioperative period.[19,22]

We believe that delay in recovery from infection can lead to the interruption of chemotherapy for the underlying disease. This can lead to ineffective treatment and hence increase the chances of relapse in the future. Upfront appendectomy in children with leukemia resulted in fewer complications, shorter hospital stay, and fewer delays in chemotherapy completion in a retrospective review by Many et al.[3] Either of the two approaches (open or laparoscopic appendectomy) can be followed based on the patient's disease status and surgeon's preferences with no significant differences in the outcome.[3]

Table 3 Details of various studies comparing study details of a similar group of patients

Study/ year	Study center	Total patients	No. of patients with appendicitis	Underlying diagnosis			Treatment			Leukemic infiltration on HPE	Outcome		
				ALL	AML	Others	Medical	Appendectomy			Recovered	Mortality	Complications
								Open	Laparoscopic				
Ver Steeg et al, 1979 [21]	Multicenter	NK	5	4	1	0	0	1	0	None	1	1	2
Angel et al, 1992 [9]	Single	2794	14	10	4	0	1	8 + 5[a]		None	11	3	0
Hobson et al, 2005 [17]	NK	464	7	5	1	1	0	6	1	None	7	0	0
Wiegering et al, 2008 [4]	Single	113	5	1	3	1	5	0	0	Unknown	5	0	0
Mortellaro et al, 2011[22]	Multicenter	NK	10	5	4	1	0	10	0	Unknown	9	1	0
Kim et al, 2012 [10]	Single	1209	7	3	4	0	0	2	5	None	7	0	0
Warad et al, 2015 [12]	Single	154	3	1	2	0	0	2	1	1	2	0	1
Wang et al, 2019 [14]	Single	NK	23	3	2	18	0	17	6	2	22	1	9
Von Mersi et al, 2021 [13]	Single	2341	21(23 episodes)	Acute leukemia 15		6	0	15	0	1		1	
This study	Single	254	6	5	1		0	6	0	None	5	1	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HPE, histopathological examination; NK, not known.
[a]Appendectomy and drainage—5, Appendectomy—8.

This study is an attempt to demonstrate the course of appendicitis in children with underlying malignancy at our institution. This study can guide the management of appendicitis in children with leukemia in a resource-constrained setting; however, it has several limitations. This is a retrospective study and the number of patients is small. The nutritional status of children as indicated by serum albumin levels should have been taken into account to correlate outcomes in this respect. We did not measure C reactive protein levels which may have helped in prognostication in this subset.

Conclusion

Acute appendicitis being the most common surgical emergency in children with hematological malignancies must always be suspected in a child presenting with persistent fever and/or pain abdomen. Diagnosing appendicitis in this subset requires good clinical and radiological acumen. Appendectomy can be safely performed in patients irrespective of neutropenia/thrombocytopenia with optimal supportive care.

Ethical Statement

Ethics approval has been obtained with their letter number DMCH/IEC/2023/216 dated 18/7/2023. 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 mentioned in the Helsinki Declaration.

Authors' Contributions

S.K., S.B., and A.G. conceptualized the study. S.K., S.B., A.G., and A.J. designed the study. S.K., S.B., A.G., A.J., C.K., and A.G. contributed to definition of intellectual content. A.G., C.K., E.J., A.J., and N.K. helped in literature search. S.K., S.B., A.G., A.J., A.G., C.K., E.J., An.J., and N.K. were involved in clinical studies and manuscript review. E.J., An.J., and N.K. were involved in data acquisition, data analysis, statistical analysis, and manuscript editing. A.G., E.J., An.J., and N.K. contributed to manuscript preparation.

Patient's/Guardian's Consent

Not applicable.

Source of Support

None.

Conflict of Interest

None declared.

Acknowledgments

None.

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Knowledge, Attitudes, and Practices regarding Pain Assessment among Nurses Working at Public-Sector Pediatric Oncology Units in Pakistan

Bashir Ahmed Khan[1] Wasfa Farooq[1] Malick Muhammed Sabih Masood[1] Muhammad Rafie Raza[1]

[1] Department of Paediatric Oncology, Indus Hospital & Health Network, Karachi, Sindh, Pakistan

Address for correspondence Bashir Ahmed Khan, BScN, Department of Paediatric Oncology, Indus Hospital & Health Network, Karachi, Sindh 75500, Pakistan (e-mail: bashir.ahmed@tih.org.pk).

Ind J Med Paediatr Oncol 2024;45:410–415.

Abstract

Introduction Pain in pediatric oncology patients is often undertreated due to a lack of timely assessment and inefficient communication between health care workers. Improper pain assessment is a leading cause of poorly managed pain in children. In high-income countries, pediatric oncology nurses play a key role in developmentally appropriate pain assessment measures to identify potential management strategies. However, nurses in low- and middle-income countries (LMICs) face a deficit of knowledge about pain assessment tools and management. Owing to differences in availability of resources, a disparity exists between health-related quality of life of cancer patients treated at public- and private-sector hospitals in Pakistan.

Methodology The Indus Hospital and Health Network partnered with nine public-sector hospitals nationwide to improve pediatric oncology practices. Supported by the My Child Matters grant, training sessions were conducted for nurses at each public-sector pediatric oncology unit (POU) from March to December 2021. Pain assessment tools were provided. To assess retention and implementation of practices, a knowledge, attitudes, and practices questionnaire was distributed online to nurses at each POU. All responses remained anonymous.

Results Fifty-four responses were recorded, 85% were female and most were between 26 and 30 years of age. Most of the participants held a diploma in nursing and were designated charge nurses with more than 6 years of experience. Forty nurses reported routinely assessing pain; the most common reason for not doing so was increased workload. Correlations were observed between routinely performing pain assessment and the number of patients per nurse, availability of formal credentialing or certifications at the institution and routinely performing pain assessment, availability of trainings focused on pain assessment and routinely performing pain assessment, and qualification of nurses and knowledge of nonpharmacological pain assessment methods.

Conclusion Strategies to improve pain assessment knowledge and practices among pediatric oncology nurses in LMICs must be developed to improve patient care and clinical outcomes.

Keywords
- attitude
- knowledge
- LMICs
- nursing
- oncology
- pediatric
- pain

article published online
June 4, 2024

DOI https://doi.org/10.1055/s-0044-1787562.
ISSN 0971-5851.

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

Introduction

Children diagnosed with cancer are particularly susceptible to experiencing pain as a result of the intensity of illness and the treatments they undergo. Despite this vulnerability, the pain experienced by pediatric oncology patients is frequently not adequately addressed, largely due to delays in timely assessment and ineffective communication among health care professionals. An overarching factor contributing to the inadequate management of pain in children is the insufficient evaluation of pain, which significantly impacts their overall quality of life and treatment outcomes.[1–3] Frequently termed the "fifth vital sign," pain necessitates assessment and documentation in conjunction with traditional vital signs such as blood pressure, pulse, temperature, and respiratory rate.[4]

For children, pain expression typically occurs through nonverbal cues and bodily responses. In such cases where a child is between the ages of 2 months and 3 years, the appropriate assessment tool is the behavioral pain scale, such as the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. In contrast, for children aged 3 years and older, self-reported pain intensity becomes more reliable. This can be measured using the Wong–Baker faces pain scale, visual analog scale, and numerical rating scale.[3,5,6]

Within high-income nations, pediatric oncology nurses take on a crucial role in formulating age-appropriate pain assessment methodologies, identifying potential avenues for pain management, and administering both pharmacological and nonpharmacological treatments.[7] Developing nations encounter a lack of understanding concerning pain assessment tools and the significance of proficiently using them.[2] In Pakistan, more than 50% of patients with advanced-stage cancer experience undertreatment of pain due to inadequate education and training of health care workers.[8] Furthermore, disparities arise in the quality of life of cancer patients treated in Pakistan's public- and private-sector hospitals due to variable resource availability.[9]

In a collaborative effort, the Department of Pediatric Hematology/Oncology (PHO) at the Indus Hospital and Health Network (IHHN) partnered with nine public-sector hospitals throughout Pakistan. This partnership was aimed at elevating pediatric oncology practices on a nationwide scale, with the objective of comprehensively enhancing childhood cancer services. Given the limited existing research, this study is designed to evaluate the knowledge, attitudes, and practices surrounding pain assessment among pediatric oncology nurses within these nine units.

Methods

Study Design

The IHHN PHO project secured the My Child Matters (MCM) grant from the Sanofi Espoir Foundation, propelling initiatives in training and capacity enhancement within partnered pediatric oncology units (POUs). An integrated approach was adopted, combining online theoretical classes with hands-on, in-person sessions for nurses across each POU. These sessions were conducted between March and December 2021. The program prioritized comprehensive pain assessment and management techniques for pediatric cancer patients.

Pertinent pain assessment tools, including the Wong-Baker faces pain scale, visual analog scale, and FLACC pain scale, were provided in both hard and soft formats to nursing leadership at each unit. To gauge the absorption and application of these resources, a structured questionnaire encompassing domains of knowledge, attitude, and practices concerning pain assessment was developed and administered to nurses at nine public-sector hospitals via an online platform.

Sample Size

Study was conducted across nine public-sector hospitals. Fifty-four nurses in total chose to participate.

Inclusion and Exclusion Criteria

The criteria for the study included nurses who were currently working in pediatric oncology and excluded those who were not.

Statistical Analysis

The collected data were analyzed using SPSS v23 for meaningful insights. Descriptive statistics were computed for quantitative variables, and frequencies and cross-tabulations were made for qualitative variables.

Ethics

Ethical approval for the study was obtained from the IHHN Institutional Review Board (IRB number: IHHN_IRB_2022_03_014) on April 8, 2022. Ethical considerations were taken into account by obtaining written informed consent from the participants and ensuring the anonymity and confidentiality of their responses. Our study complied with the Declaration of Helsinki.

Results

A total of 54 nurses, distributed across different age groups were participated in the study. Most participants (61.1%) fell within the age range of 26 to 30 years, indicating a relatively young nursing workforce. The age group of 31 to 40 years accounted for one-third of the participant population, while a very minor number were between 20 and 25 years of age and above 40 years of age.

Gender distribution revealed that the sample was predominantly female (85.2%).

Approximately two-thirds of the nurses held a diploma in nursing (63.0%), while one-third held a bachelor of science in nursing degree (33.3%). Less than 2% of participants held higher qualifications, which included a master of science in nursing and a diploma in pediatric oncology nursing.

The work experience of the nurses varied, with the largest group (42.6%) having more than 6 years of experience. Approximately one-third (29.6%) had 4 to 6 years of experience, while the rest had less than 3 years of experience.

One-third (31.45%) of the nurses who participated in this study reported having access to ongoing training in pain assessment in the form of Continuing Nursing Education (CNEs), whereas approximately two-thirds (66.7%) did not. The fact that only five nurses (9.3%) mentioned formal training in pain management suggests that institutional credentialing programs in this area are limited.

Only 32 nurses (59.3%) were acquainted with the numeric pain scale, which is a widely utilized pain assessment tool. A larger subset of nurses (38 nurses, 70.4%) demonstrated awareness of the facial pain scale. In contrast, a smaller cohort of 11 nurses (20.4%) were familiar with the FLACC scale, a behavioral pain assessment tool often employed for children older than 2 months and younger than 3 years.

Within our study, among the nurses who conducted initial pain assessments, 16 nurses (42.1%) reported actively engaging in pain reassessment, while 22 nurses (57.9%) did not consistently perform follow-up pain evaluations. Among those who did not engage in routine pain reassessment, several reasons emerged, including the perceived lack of importance in 1 nurse (4.5%), insufficient availability of resources/forms indicated by 9 nurses (40.9%), and the formidable challenge of managing workload highlighted by 12 nurses (54.5%).

Knowledge

As shown in ►**Table 1**, when assessing knowledge, there was an association found between a nurse's work experience and their familiarity with pain assessment tools such as facial pain scale (p-value = 0.0005) and numeric pain scale (p-value = 0.005). An association was also seen between work experience and knowledge of nonpharmacological pain management interventions; however, according to our study, nurses with less experience were more likely to know about it than their more experienced counterparts.

Attitudes

As shown in ►**Table 2**, most nurses reported that they assessed pain but were less likely to reassess pain or document their assessment. Lack of resources/forms and workload were often cited as the reasons.

Practices

As shown in ►**Table 3**, most nurses demonstrated a lack of implementation of pain assessment methods regardless of their work experience level.

As shown in ►**Fig. 1**, only 29.6% nurses in the study had a nurse-to-patient ratio of 1 to 5, which is considered a favorable nurse-to-patient ratio, whereas the rest of the study participants had a higher nurse-to-patient ratio.

Discussion

The assessment, management, and reassessment of pain in childhood cancer patients are primarily the responsibility of oncology nurses.[2] Regardless of treatment outcomes, the efforts of pediatric oncology nurses to identify and manage a child's pain have the potential to improve the quality of life both of patients and their families.[7] Effective pain management for children and adolescents faces continued obstacles; a major one being the lack of knowledge plaguing health care professionals such as nurses, particularly in low- and middle-income countries (LMICs).[10]

The population of nurses in this study highlighted a female predominance which aligns with findings from a comparable survey conducted in Iran, in which 79.8% of the nurses were women.[11]

CNE and specialized training programs are crucial to nurses' pain evaluation and management skills. They show a commitment to professional development and keeping health care workers abreast of new practices. Only one-third nurses (31.5%) said their hospitals offered pain assessment CNE or training, while the rest either report the lack of such programs. This is especially shocking since according to the Baseline Nursing Standards, pediatric oncology nurses must complete 9 hours of CNE annually.

Traditional clinical practice can hinder pain management by failing to consistently assess and document pain. This is made worse by a lack of feasible treatment techniques, and the belief that pain is expected and is therefore trivial. Health care organizations and institutions must go beyond teaching to improve resource distribution and assessment to maintain good pain management practices. Health care settings can

Table 1 Nurses recognized pain as the fifth vital sign

	Nurse's work experience				
	< 1 y	1–3 y	>3 y	Total	p-Value
Recognized pain as the fifth vital sign, n (%); $n = 54$	6 (11%)	7 (13%)	33 (61%)	46 (85%)	0.9775
Nurses' familiarity with pain control modalities					
Pharmacological pain management, n (%); $n = 54$	6 (11%)	7 (13%)	37 (67%)	50 (93%)	1.081
Nonpharmacological pain management, n (%); $n = 54$	4 (7%)	6 (11%)	6 (11%)	16 (30%)	0.0008
Nurses' familiarity with pain assessment tools					
FLACC scale, n (%); $n = 54$	0 (0%)	1 (2%)	10 (19%)	11 (20%)	0.2376
Facial pain scale, n (%); $n = 54$	1 (2%)	6 (11%)	31 (57%)	38 (70%)	0.0005
Numeric pain scale, n (%); $n = 54$	1 (2%)	3 (6%)	28 (52%)	32 (59%)	0.005

Abbreviation: FLACC, Face, Legs, Activity, Cry, and Consolability.

Table 2 Attitudes of Nurses towards Pain Assessment

	Nurse's work experience				
	< 1 y	1–3 y	>3 y	Total	*p*-Value
Routine pain assessment, *n* (%); *n* = 54	6 (11%)	6 (11%)	26 (48%)	38 (70%)	0.344
Pain reassessment following any intervention, *n* (%); *n* = 38	1 (3%)	5 (13%)	10 (26%)	16 (42%)	0.074
Pain assessment documentation, *n* (%); *n* = 38	3 (8%)	4 (11%)	14 (37%)	21 (55%)	0.783
Reasons for not documenting patient's pain score					
It is not important, *n* (%); *n* = 17	1 (6%)	0 (0%)	0 (0%)	1 (6%)	
Lack of resources/forms, *n* (%); *n* = 17	1 (6%)	2 (12%)	4 (24%)	7 (41%)	
Workload, *n* (%); *n* = 17	1 (6%)	0 (0%)	8 (47%)	9 (53%)	
Reasons for not reassessing the patient for pain					
It is not important, *n* (%); *n* = 22	1 (5%)	0 (0%)	0 (0%)	1 (5%)	
Lack of resources/forms, *n* (%); *n* = 22	0 (0%)	3 (14%)	6 (27%)	9 (41%)	
Workload, *n* (%); *n* = 22	0 (0%)	4 (18%)	8 (67%)	12 (55%)	

Table 3 Pain assessment methods used

	Nurse's work experience				
	< 1 y	1–3 y	>3 y	Total	*p*-Value
Use of standardized pain assessment tools, *n* (%); *n* = 54	2 (5.2%)	6 (16%)	17 (45%)	25 (66%)	0.05156
Use of interviews for pain assessment, *n* (%); *n* = 38	3 (8%)	3 (8%)	6 (16%)	12 (32%)	0.2523
Use of other methods for pain assessment, *n* (%); *n* = 38	1 (3%)	0 (0%)	0 (0%)	1 (3%)	0.06465

enhance pain evaluation and management by addressing these issues, in the process improving patient care and outcomes.[12]

As shown in ►**Table 1**, a significant majority of nurses (87.0%) recognized pain as the fifth vital sign, mirroring findings from a parallel survey in Brazil where 79.3% of nurses reported a similar acknowledgment.[13] However, this study shows that there were certain gaps in knowledge regarding specific pain assessment tools. A large subset of nurses were familiar with the facial pain scale, but slightly more than half (59.3%) were acquainted with the numeric pain scale, and only a quarter (20.4%) was familiar with the FLACC scale. Effective pain management commences with accurate pain assessment and the utilization of standardized tools. These tools are instrumental in evaluating the effectiveness of interventions tailored to the individual needs of patients, particularly concerning pain relief.[14] Recent literature also highlights this disparity between recommended methods of frequent pain evaluation and their lack of usage and implementation on the ground.[12]

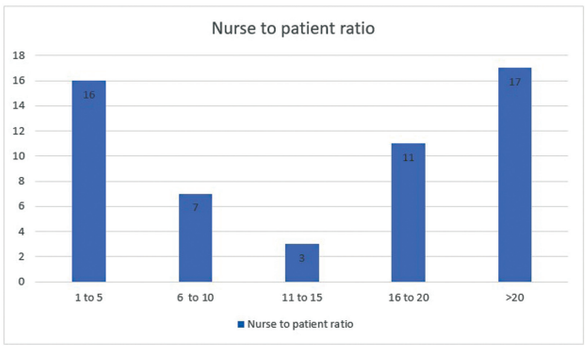

Fig. 1 Distribution of Nurse-to-Patient Ratios Among Study Participants.

Most nurses (92.6%) exhibited familiarity with pharmacological approaches for pain management, whereas awareness of nonpharmacological pain control methods such as complementary therapies and relaxation techniques was less prevalent (29.6%). Nurses with less experience were more likely to know of nonpharmacological methods, which may point toward a change in emphasis in nursing teaching programs in recent times or suggest that more experienced nurses tend to forget about them with the passage of time due to a lack of implementation. Interestingly, a study conducted in Zimbabwe found that most respondents demonstrated knowledge of nonpharmacological pain control methods. This discrepancy in awareness regarding nonpharmacological approaches highlights the need for comprehensive education and training initiatives to ensure that nurses are equipped with a diverse set of pain management strategies. Addressing this knowledge gap can enhance the ability of health care professionals to provide well-rounded and patient-centered pain management.[15]

As shown in ►**Table 2**, two-thirds of nurses (70.4%) demonstrated the positive practice of routinely conducting

pain assessments concurrently with vital sign measurements. This proactive approach within patient care underscores the significance of comprehensive pain management. Conversely, one-third of nurses (29.6%) indicated that they did not consistently incorporate pain assessment into their routine practices. It is imperative for health care professionals to consistently evaluate pain, particularly considering that many patients may not spontaneously report pain unless specifically prompted. Thus, the practice of patient-centered pain assessments aligns with the core principles of patient care, emphasizing the necessity of incorporating pain assessment as a routine component of health care delivery.[16]

The documentation of pain scores among participating nurses showed variability. Some nurses reported actively documenting pain scores, while others did not routinely record them. Barriers to comprehensive pain assessment documentation were identified, including a perceived lack of importance, limited availability of resources/forms, and the challenge of managing heavy workloads. These findings underscore potential hurdles in effectively integrating pain assessment documentation into clinical practice. The importance of pain reassessment after interventions cannot be understated, as it forms the cornerstone of evaluating the efficacy of pain management strategies.

Close to half of our study population (42.1%) performed initial pain assessments which parallels the findings in a study conducted in Uganda. In their study, documentation of pain assessment was commonly reported, reflecting the recognition of pain as an essential vital sign. However, their results also suggested that while pain assessment may be documented, it might not be effectively discussed in nurses' reports. This highlights a potential gap between documenting pain assessment and translating these findings into actionable care decisions. Such disparities between documentation and effective communication of pain assessment results emphasize the need for cohesive strategies to ensure that pain assessment is not only recorded but also integrated into the broader patient care process.[14,17]

As shown in ►**Table 3**, a significant number of nurses (65.8%) used standardized pain scales such as the facial pain scale, and one-third (31.6%) preferred conversational nonstandard interviews. This aligns with findings from a comparable survey conducted in Jerusalem, Israel.[18] These findings support the literature outlining the gap between current guidelines recommending regular and routine pain evaluation using valid and reliable methods.[12]

As shown in ►**Fig. 1**, only one-third of the study participants (29.6%) reported that they were responsible for managing one to five patients, reflecting a favorable nurse-to-patient ratio that promotes personalized care. The rest managed 6 or more patients along with a shocking one-third of participants (31.5%) managing more than 20 patients per shift. This is similar to a study conducted in Brazil, in which it was identified that the highest patient-to-nurse ratio was around 27 patients per nurse during shifts. This congruence in findings between our study and the Brazilian study underscores the challenges faced by health care systems in LMICs in maintaining optimal nurse-to-patient ratios, particularly in settings like pediatric oncology where the demands for comprehensive and individualized care are paramount.[19]

Most people who answered our survey cited an excessive amount of work and a dearth of resources as the primary reasons why comprehensive pain evaluations and recordings were not performed frequently and on each patient. This issue is further exacerbated by the fact that Pakistan has only 0.49 registered nurses for every 1,000 people, resulting in a severely understaffed health care system (Pakistan Human Resources for Health Vision 2018–2030). Therefore, significant changes will need to be made to Pakistan's health care system to address the challenges posed by its deteriorating infrastructure and limited supply of resources.[20,21]

As evidenced by this study, nurses working in POUs within the public sector in Pakistan encounter a range of barriers when it comes to evaluating and managing pain in a clinical setting. These challenges include a lack of knowledge, a severe shortage of human resources, inadequate availability of materials, and significant deficiencies in leadership support, among various other microlevel issues. In light of these challenges, it is crucial to recognize that oncology nurses are uniquely positioned to emphasize the importance of accurate and frequent pain assessment for their patients. They play a pivotal role in advocating for the necessity of comprehensive pain evaluation until the patient's pain is effectively alleviated.

Limitations

Several limitations are inherent in this study. As a cross-sectional investigation, it captured a singular perspective of nurses' knowledge, attitudes, and practices within a specific time frame. Longitudinal studies would offer a more dynamic understanding of the evolution of pain assessment practices over time. Furthermore, the study was confined to nurses functioning within public-sector POUs within specific Pakistani cities. Consequently, the generalizability of the findings to nurses in distinct health care settings or geographical regions may be restricted.

Conclusion

The findings of this study highlight the need for further training in pain assessment and management for pediatric oncology nurses within Pakistan's public-sector hospitals. To address challenges such as high workload, resource limitations, inadequate training, and education in pain management, and to prioritize effective pain control in pediatric oncology as a fundamental quality care indicator, the active engagement of hospital leadership and policymakers is crucial.

Authors' Contribution

B.A.K. contributed to conceptualization, design, definition of intellectual content, literature search, data acquisition, and manuscript preparation. W.F. contributed to data analysis, statistical analysis, and manuscript editing. M.M.S.M. reviewed and edited the manuscript. M.R.R. reviewed the manuscript.

Declaration and Statement

We confirm that the manuscript has been read and approved by all named authors, that the requirements for authorship have been met, and each author believes that the manuscript represents honest work. There were no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Patient Consent

Patient consent was not required for this study as it involved surveying nurses and did not include direct patient data.

Source of Funding

None declared.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank Dr. Vashma Junaid, Dr. Misbah Baig, Dr. Natasha Baig, Dr. Rabel Gul, and Dr. Samarah Usman for their valuable guidance and support throughout this research project. We also extend our gratitude to the participants who generously shared their time and insights. This work was supported by the My Child Matters (MCM) grant by the Sanofi Espoir Foundation.

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Prospective Observational Study on the Risk Factors of Chemotherapy-Induced Myelosuppression and Its Management in a Tertiary Care Hospital

D. Keziah[1] M. Bindhiya[1] M. Jayaprakash[1] Rodrigues A. Prudence[2]

[1] PSG College of Pharmacy, Coimbatore, Tamil Nadu, India
[2] Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India

Address for correspondence Keziah D., Pharm D (continuing), 21 PPS Colony, Anna Nagar, Coimbatore south – 641004, Tamil Nadu, India (e-mail: projectcim218@gmail.com).

Ind J Med Paediatr Oncol 2024;45:416–421.

Abstract

Introduction Myelosuppression is a commonly observed dose-limiting side effect of majority of chemotherapeutic drugs, characterized by a decrease in blood cell production. They cause neutropenia, thrombocytopenia, and anemia and can be life threatening in few susceptible individuals. Attempts to lessen chemotherapy-induced myelosuppression have been minimally effective. Managing myelosuppression has been a challenge to medical practitioners and pharmacist. Identifying their risk factors and the management strategies can help prevent the debilitating effects on chemotherapy patients.

Objectives The aim of this study was to determine the risk factors for chemotherapy-induced myelosuppression and identify its management in a tertiary care hospital. We also observed the cycle it predominantly occurs and its prevalence rate in the region.

Materials and Methods The study is a prospective observational cohort study conducted in a tertiary care hospital in Coimbatore, Tamil Nadu. The sample size was calculated using RAO software for a study duration of 4 months from 73 patients who were prescribed the inclusion criteria drugs paclitaxel, carboplatin, 5-fluorouracil, doxorubicin, and cyclophosphamide. The complete blood count was obtained and followed up to find myelosuppression occurrence on day 8 of first three cycles. The National Cancer Institute grading system was used to assess the severity of myelosuppression. It was done from May 2022 to August 2022. Chi-squared tests and percentages were adopted by using the SPSS software.

Result The result for primary objective is that among the total 73 patients employed, 30 patients were found to be myelosuppressive (41%) and the prevalence rate was 41%. Risk factors such as age, gender, and diagnosis showed statistically significant association (confidence interval: 95% and p-value <0.005). The drugs paclitaxel, carboplatin, 5-fluorouracil, cyclophosphamide, and adriamycin proved to be highly myelosuppressive with a p-value of 0.049.

The results for secondary objectives were that cycle 1 was reported to be highly myelosuppressive with 27%. The treatment options that was highly used was

Keywords

- chemotherapy-induced myelosuppression
- myelosuppression
- risk factors
- myeloprotective agents
- complete blood count

article published online
July 5, 2023

DOI https://doi.org/10.1055/s-0043-1770905.
ISSN 0971-5851.

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

granulocyte-colony stimulating factor (90%), followed by packed red blood cell transfusion (7%).

Conclusion The incidence of chemotherapy-induced myelosuppression from this study showed that it was important to monitor the complete blood count levels in patients undergoing chemotherapy. Early assessment of risk for developing myelosuppression may prevent or reduce its severity.

Introduction

Cancer is a group of diseases, where some of the body's cells grow uncontrollably and spread in the body. Cancer is among the leading causes of death worldwide. According to National Cancer Institute (NCI) in 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide; accounting for nearly 10 million deaths in 2020. Chemotherapy is treatment of cancer with drugs that uses powerful chemicals to kill fast growing tumor cells in your body. There are many different chemotherapy drugs that are used alone or in combination to treat different types of cancers.[1] In chemotherapy, drugs interfere with DNA synthesis and mitosis to destroy the cancer cells. Hence, it is not only effective to treat most types of cancers, but also possesses a series of side effects. These chemotherapy side effects may be mild and treatable or can cause life threatening complications.

Chemotherapy-induced myelosuppression (CIM) is the most common dose-limiting and fatal complication of cancer treatment. Myelosuppression is caused by destruction of proliferating progenitor cells that produce mature red and white blood cells and platelets in peripheral circulation. As immature cells in the marrow are destroyed, pre-existing mature cells are eliminated, and the nadir of the individual's blood cell count is attained. At that time, cells are maturing and are ready to release into peripheral blood so within a short period the blood count has returned to near normal state and the next dose of chemotherapy is administered.[2]

Myelosuppression is a crucial factor in determining how much drug is to be given. After treatment has begun, if bone marrow has not recovered before the next cycle of chemotherapy, dosage reduction or delay starting the cycle will depend primarily on intent of treatment.[3] *If the patient is in a clinical trial,* the grade of toxicity will correspond with appropriate course of action. According to NCI grading scale, myelosuppression is graded, and the type is decided. Myelosuppression is the umbrella term for anemia, thrombocytopenia, and neutropenia.[4] Grade I myelosuppression may require no modification in the treatment plan, whereas a grade III or IV toxicity may require not just a delay in treatment but dose reduction, depending on the outcome.[5] Transfusions of packed red blood cells (PRBC) and platelets are common treatments when chemotherapy causes anemia and thrombocytopenia.[2]

The granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage-colony stimulating factors (GM-CSF) reduce the severity and duration of neutropenia after therapy. Antibiotics are given to prevent infection.[6] Regular peripheral blood count monitoring is the standard practice. The other mainstay of early detection is education of patients, caretakers, and healthcare staff with the signs and symptoms suggestive of cytopenia's, and importance of prompt blood count confirmation and appropriate management. Dose reduction or delay before scheduled courses maybe suggested if unexpectedly severe or prolonged cytopenia occur. Primary or secondary prophylaxis happens by giving G-CSF.[7]

In this study, the association of risk factors (age, gender, body surface area, comorbidities and chemotherapeutic drug combinations) with myelosuppression is studied. To identify myelosuppression, data from complete blood count (CBC)-platelets, RBC and white blood cells along with absolute neutrophil count (ANC) were noted on the day 8 and the nadir day reports.[8] The risk factors of CIM were studied using five chemotherapeutic drugs that are commonly used in chemotherapy (paclitaxel, carboplatin, cyclophosphamide, doxorubicin, and 5-fluorouracil).[9]

Therefore, this study aims to serve as a resource for healthcare professionals to enhance their understanding of myelosuppression and its regular monitoring in patients receiving chemotherapy. The primary objective of our study is to determine the prevalence rate of myelosuppression and its risk factors in cancer patients. The secondary objective was to identify the cycle in which increased myelosuppression occurs and the treatment options used.

Materials and Methods

The study is a prospective observational cohort study conducted in a tertiary care hospital in Coimbatore, Tamil Nādu. The sample size of 73 was calculated using the RAO software from data obtained by daily patient flow and study duration. The study was carried out for a duration of 4 months, and data was collected from patients who were prescribed with the inclusion criteria drugs paclitaxel, carboplatin, 5-fluorouracil, doxorubicin, and cyclophosphamide. The CBC was obtained and followed up to find myelosuppression occurrence on day 8 of blood reports, since the administration of drug for the first 3 cycles. The NCI grading system was used to assess the severity of myelosuppression of carboplatin, paclitaxel, 5-fluorouracil, adriamycin, and cyclophosphamide. The study was done from May 2022 to August 2022. Chi-

squared tests and percentages from SPSS software were used for statistical analysis. The result for primary outcome is that among the total 73 patients employed, 30 patients were found to be myelosuppressive (41%) and the prevalence rate was 41%. Risk factors such as age, gender, and diagnosis showed statistically significant association (confidence interval: 95% and p-value <0.005). The drugs paclitaxel, carboplatin, 5-fluorouracil, cyclophosphamide, and adriamycin proved to be highly myelosuppressive with a p-value of 0.049. The results for secondary outcome were that cycle 1 was reported to be highly myelosuppressive with 27%. The treatment options that was highly used was granulocyte-colony stimulating factor (90%), followed by packed red blood cell transfusion (7%).

Inclusion Criteria

- All types of cancer with chemotherapy drugs (paclitaxel, carboplatin, cyclophosphamide, 5-fluorouracil, and doxorubicin) in weekly and 3 weekly dosage regimens.
- >18 years of age.
- Cancer patients in cycles 1, 2, and 3.

Exclusion Criteria

- Patients who are not receiving chemotherapy.
- Psychiatry patients with cancer.
- Cycles excluding 1, 2, and 3 due to difficulty to obtain data and patient follow-up.
- Patients receiving concurrent chemotherapy and radiation therapy.

Statistical Analysis

The data were entered in Ms excel spread sheet and analyzed using Statistical Package for Social Science (SPSS) version 26.0. Qualitative and Quantitative variables were compared and analyzed using chi-squared test.

Ethics

The study was approved by Institutional Human Ethics Committee, PSG hospitals, Coimbatore, Tamil Nadu, India. (Approval no: PSG/IHEC/2022/Appr/Exp/118; approved on May 04, 2022). 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

In this study, 73 patients were recruited based on their inclusion and exclusion criteria. The age wise distribution was found by grouping the patients according to World Health Organisation (WHO) scale as age groups (15–24) with 6%, age group (35–64) with 71%, and more than 65 years with 23%. The gender wise distribution showed 21% male and 80% female in the study. The study categorized the body mass index (BMI) for patients in C1, C2, and C3. The BMI was categorized as less than 18.5 (underweight), 18.5 to 24.9 (normal range), 25 to 29.9 (overweight) and more than 30 (obese). The highest distribution of myelosuppression was in the BMI range 18.5 to 24.9 (normal range) as 48% ($n=35$).

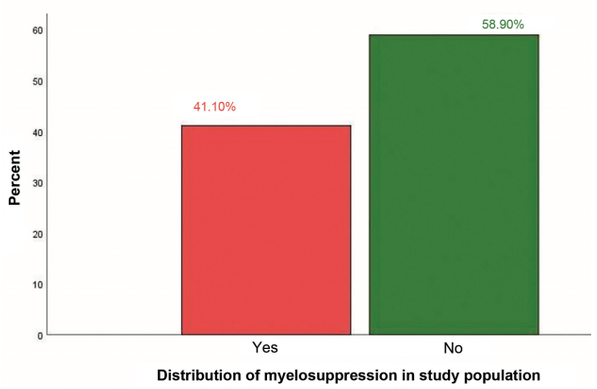

Fig. 1 Occurrence and nonoccurrence of myelosuppression in study population.

In this study, among the total population the social history was taken into accounted and 10% ($n=7$) patients were smokers, 4% ($n=3$) were alcoholics, and 3% ($n=2$) were smokers and alcoholics. The past medical history showed diabetes mellitus (DM) 27% ($n=5$), hypertension (HTN) 6% ($n=4$), both DM 2 and HTN 14% ($n=10$), no comorbidities 56% ($n=41$), and no past medical history as 18% ($n=13$). The past medication history, chemotherapy, and oral hypoglycemic agents (OHA) showed 7% ($n=5$), chemotherapy, and anti-HTN showed 6% (n = 4), chemotherapy, OHA, anti-HTN combined showed 14% ($n=10$), chemotherapy alone showed 56% ($n=41$), and none showed 18% ($n=13$). Family history was also included based on genetic lineage.

Among 73 patients, 41% ($n=30$) were found to have myelosuppression (►**Fig. 1**). The objective was met by calculating the prevalence rate by,

$$\text{Prevalence rate} = \frac{\text{no. of new cases of myelosuppression}}{\text{total study population}} \times 100$$

$$= \frac{30}{73} \times 100$$

$$= 41\%$$

The occurrence of myelosuppression in the population was 41% ($n=30$). ►**Table 1** shows the relationship of myelosuppression with gender, age, and disease condition in this study. Also, other postulated risk factors like BMI, past medical and medication history, social history, and family history did not show significant statistical association. In this study, a total of 30 patients got myelosuppression among which grade 1 was 27% ($n=20$), grade 2 was 10% ($n=7$), grade 3 was 11% ($n=8$), grade 4 was 3% ($n=2$), and prophylaxis was given for 3% ($n=2$). The highest distribution was in grade 1 with 27% ($n=20$).

The cycle in which CIM occurred more was cycle 1 with 56% followed by other cycles (►**Fig. 2**). Additionally, grades of

Table 1 Significance of risk factors associated with myelosuppression in study population

Risk factors	*p*-Value
Gender	0.048
Age	0.046
BMI C1	0.313
BMI C2	0.386
BMI C3	0.654
Social history	0.674
Family history	0.406
Past medical history	0.343
Past medication history	0.343
Diagnosis	0.048
Drugs	0.049

Abbreviations: BMI, body mass index; C1, cycle 1; C2, cycle 2; C3, cycle 3.

myelosuppression were assessed according to NCI guidelines. The management strategy used in the tertiary care center for the myelosuppressive patients with myeloprotective agents were found to be G-CSF, PRBC transfusion, and a combination of both. The myeloprotective agent G-CSF 90% was prescribed the most (►**Fig. 3**).

Discussion

CIM is a life-threatening condition and commonly manifests as anemia, neutropenia, and thrombocytopenia and often results in an increased risk of infections, shortness of breath, fatigue, and excessive bleeding.

In this study of chemotherapy patients, female patients (80%) have reported to have more myelosuppression than men (20%). According to Nan Jiang et. Al and WHO Female gender are scientifically proven to have an increased 35% risk of developing side effects than men due to sex differences in inflammatory and immune responses.[10] Many biological differences in male and female in patterns of cancer are due to differences in their sex hormones, such as estrogenic or testosterone.

Age group of 25 to 65 (60%) reported to be more myelosuppressive than other groups of 19 to 24 and seniors of age above 65, similar to the study of Repetto.[3,11] Complications due to age-related physiologic changes that can increase the toxicity are decreased stem cell reserves, decreased ability to repair cell damage, progressive loss of body protein, and accumulation of body fat.[12]

Body weight was reported to have increased risk of developing several cancers including colorectal cancer, breast cancer, renal cell, and pancreatic cancer from studies.[13] One proposed mechanism in increased risk of developing cancer was the reduction in growth factor production with increased body weight. This study showed an increase in myelosuppression in patients who fell under the BMI groups 18.5 to 24.9 and 25 to 29.9, with strong support from the study of Weycker et al.[14] BMI classification was done according to standard WHO classification.

Social history denoted as smoking, alcohol consumption, and other substance use were collected in this study. According to the study of Beyth et al,[15] cigarette smoking was linked to significant decrease in bone marrow concentration of mesenchymal stem cells. In this study, social history was not found to have any relationship with CIM.

Family history consists of the collection of information about the patients and their family members devoted to an understanding of heritable lines. Many diseases have genetic

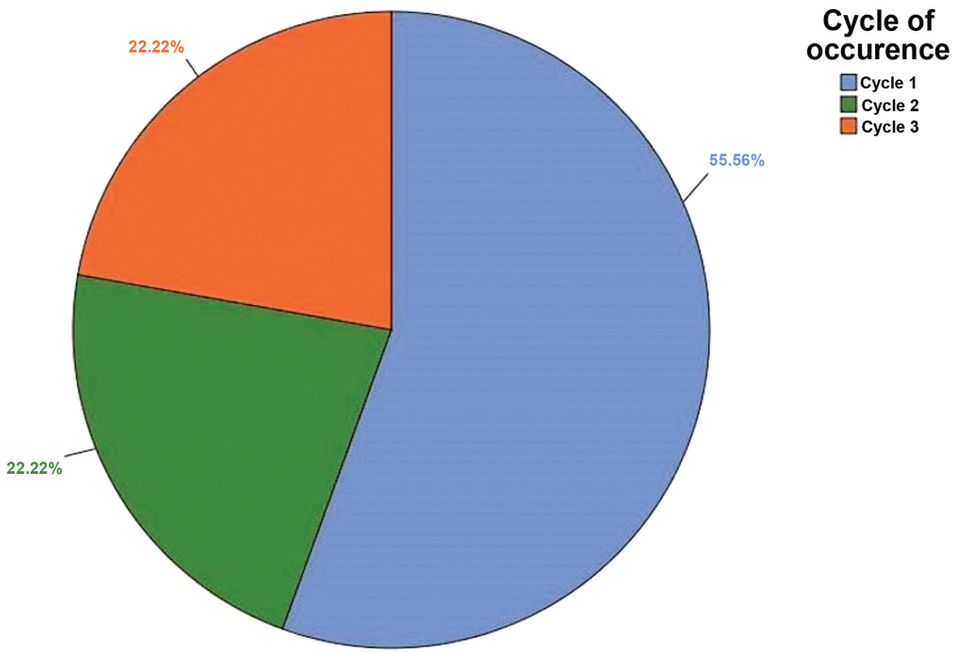

Fig. 2 Cycle wise incidence of myelosuppression in study population.

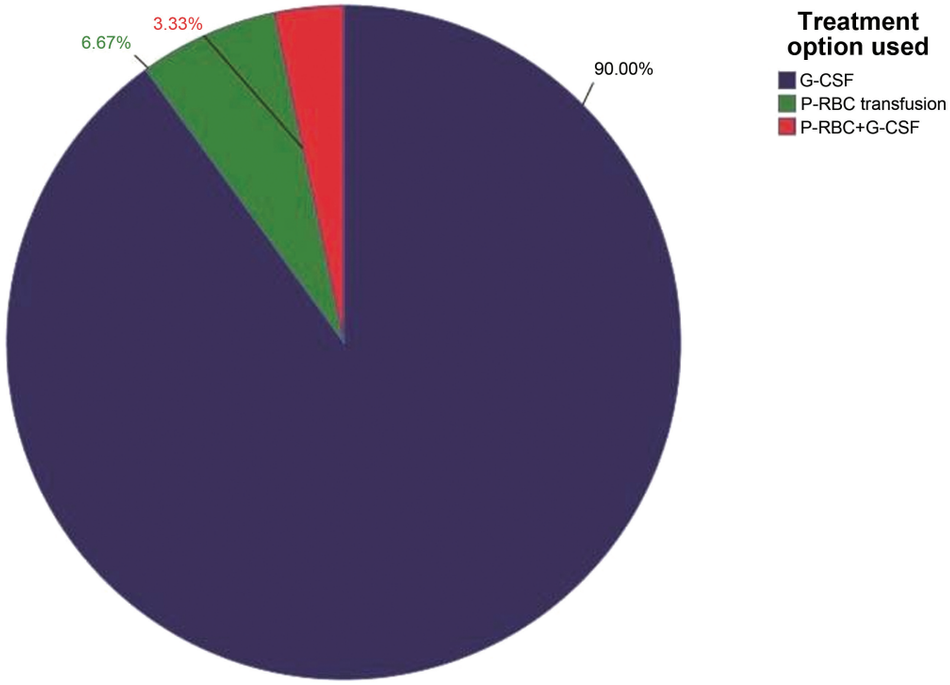

Fig. 3 Myeloprotective class percentage used to treat myelosuppression. G-CSF, granulocyte colony-stimulating factor; PRBC, packed red blood cell.

lineage proposing as one of the significant risk factors. Family lineage of diseases like diabetes and HTN and others were not found to be a significant risk factor for CIM in this study.

Medical history denoted the comorbid conditions that coexisted with the primary disease. Given that most of the cancers are diagnosed, these comorbid conditions are preexisting. Examples of comorbid conditions are DM, HTN, cardiovascular diseases, liver diseases, kidney problems, etc. Some of these have common risk factor with cancer. The type and severity of comorbidity may affect treatment outcomes and hence require customization. In this study, comorbid conditions of patients were not found to have significance in causing CIM.

Medication history is the class of drugs given other than chemotherapy drugs in this study. Medication history is proposed to have impact on the occurrence of adverse event due to polypharmacy. Other drugs found to cause myelosuppression are chloramphenicol, Meclofenamic acid, quinidine, trimethoprim-sulfadiazine, and other antifungals. In this study, medication history was found to be an insignificant risk factor to cause CIM.

Breast cancer has been the disease that has reported to show more myelosuppression in our study. Breast cancer has only been seen in woman and no male breast cancer cases were reported in this study. Evidence from several studies showed that woman have more risk of developing adverse reaction to chemotherapy. Women have 100 times greater risk of developing breast cancer due to presence of more breast cells than male. Other factors like race and ethnicity, menstrual cycle, lifestyle changes, and use of contraception can influence the development of myelosuppression in breast cancer.

Drugs in this study are the inclusion criteria drugs, that is, paclitaxel, carboplatin, cyclophosphamide, 5-fluorouracil, and doxorubicin. Cell cycle specific and cell nonspecific drugs are reported to cause rapid myelosuppression that is rapid and recovery is quicker, whereas cell noncycle specific causes myelosuppression that is delayed, prolonged and cumulative with evidence from study of Maxwell and Maher.[1] The same has been reported in our study with 41%.

WBC nadir occurs during every cycle of chemotherapy in patients. Nadir occurs in chemotherapy patients alone or in combination around 8 to 14 days of chemotherapy drugs intake with reference to Barreto et al.[16] Also, myelosuppression can occur in any cycle and it is due to large intrasubject variability. In this study the cycle that shows increased myelosuppression was cycle 1 with 56% followed by cycle 2 and cycle 3, after follow-up of individual patients with their CBC reports.

In this study, gender, age, disease condition, and inclusion criteria drugs (paclitaxel, 5-fluorouracil, carboplatin, cyclophosphamide, and adriamycin) were found to be significant risk factors in the development of myelosuppression.

Limitations

The study was performed in a single-center hospital that resulted in homogenous sample intake. The follow-up of patient's files and collecting sample details were difficult, due to record unavailability. Patient flow was affected due to coronavirus disease 2019 pandemic. Febrile neutropenia patients were not included in this study.

Conclusion

The incidence of CIM from this study showed that it was important to monitor the CBC levels in patients undergoing chemotherapy. Early assessment of risk for developing myelosuppression may prevent or reduce its severity. Drugs prescribed like paclitaxel, carboplatin, cyclophosphamide, and doxorubicin have increased risk of causing myelosuppression. Assessment and prevention of CIM should be considered as one of the important aspects in clinical practice because negligence of monitoring CBC profile may lead to life threatening situations.

Pharmacist can improve appropriate medical care to reduce occurrence of myelosuppression. Dose titrations, capping, prophylactic treatments, and medical intervention provided by pharmacists can be valuable in reducing the harm of chemotherapy adverse effects. Medication chart review, follow-up, and checking for adverse drug reactions aid the process. Further suggesting predictive models allowing better access to a patient's susceptibility to antineoplastic agent-induced myelotoxicity will enable better individualized therapy thought to be unpredictable. Finally, the use of modern novel therapies and molecular information can help mitigate the lethal risks of chemotherapy induced myelotoxicities in hospital setup.

Authors' Contributions

Keziah, Bindhiya, and Jayaprakash were involved in concept, design, definition of intellectual content, literature search, data acquisition, statistical analysis, manuscript editing, and manuscript preparation. Prudence A Rodrigues helped in clinical studies, data analysis, statistical analysis, and manuscript review. The manuscript has been read and approved by all authors and all the requirements have been met.

Conflict of Interest

None declared.

Acknowledgement

We would like to thank PSG Hospitals for providing facilities to carry this study. We also thank department of oncology and other colleagues who supported us throughout. No funding was required to carry out this study.

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Histopathological Study of Gastric Adenocarcinoma with Special Reference to Expression of HER2/neu and Ki-67 Assessed by Immunohistochemistry

Saiqa Nisar[1] Sukla Naskar[2] Saumitra Biswas[3]

[1] Department of Pathology, Suri Sadar Hospital, Birbhum, West Bengal, India
[2] Department of Pathology, Murshidabad Medical College, Murshidabad, West Bengal, India
[3] Department of Pathology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India

Address for correspondence Saiqa Nisar, MD Pathology, Suri Sadar Hospital, Birbhum, West Bengal 731101, India (e-mail: nisar.saiqa@gmail.com).

Ind J Med Paediatr Oncol 2024;45:422–429.

Abstract

Introduction Gastric cancer has become the third leading cause of cancer deaths globally. It accounts for 5.7% of cancer around the world, with a rate of mortality around 8.2%. Evaluation of human epidermal growth factor receptor 2 (HER2)/neu overexpression for targeted therapies is presently the mainstay of treatment in gastric cancer. High Ki-67 index expression in gastric cancer is an indicator of poor prognosis.

Objectives To study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma and to determine the correlation between HER2/neu expression and Ki-67 index.

Materials and Methods This is a prospective study in a tertiary care hospital, Kolkata from January 2019 to June 2020. Gastrectomy and endoscopic biopsy of gastric adenocarcinoma were studied for histopathology and immunohistochemistry (HER2/neu and Ki-67 index). Statistical analysis used: SPSS (version 21.0, IBM, Chicago, Illinois, United States) for windows software.

Results Among 54 cases, most of them were intestinal type, antral, moderately differentiated, stage III cases. HER2 expression and high Ki-67 index were observed in 28.0 and 40.75% cases, respectively. Statistically significant correlation was found in both HER2 expression and high Ki-67 index with location of the tumor and pathological nodal (pN) stage. A positive correlation was found between HER2/neu score and Ki-67 index ($p = 0.007$) (correlation coefficient = 0.4).

Conclusion A positive correlation was found between HER2/neu positivity and high Ki-67 index, both were associated with higher pathological tumor stage and pN stage. So, advanced cases may be considered for targeted therapy using trastuzumab.

Keywords
- gastric adenocarcinoma
- HER2/neu
- Ki-67 index
- trastuzumab

article published online
July 18, 2024

DOI https://doi.org/10.1055/s-0044-1788308.
ISSN 0971-5851.

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

Introduction

Gastric cancer ranks third globally in terms of overall cancer mortality, trailing only colorectal and lung cancer, according to GLOBOCAN[a] 2018 data. Among all cancers, gastric cancer has the fifth highest incidence, accounting for 5.7% of newly diagnosed cases.[1,2] Ten percent of deaths caused by cancer globally are attributable to gastric carcinoma (GC), which has a 70% case fatality rate.[3]

Males are more likely to develop gastric cancer. In developed countries, men have 2.2 times greater likelihood than women to get diagnosed with stomach cancer. The ratio in developing countries is 1.83.[1] Although most patients are older than 50 years, rare cases arise in younger individuals and even children.[4]

Early-stage cancers are typically treated with surgical resection; however, the majority of patients get diagnosed when the disease has advanced and is frequently incurable. Despite chemotherapy, the outcome for patients with advanced resectable stomach cancer is still pathetic. Therefore, early tumor detection and the use of molecular targeted therapy can increase patient survival by reducing the risk of recurrence and metastasis.[2,3]

In gastric cancer, overexpression of human epidermal growth factor receptor 2 (HER2)/neu plays a pathogenetic, therapeutic, and predictive role. One of the mainstays of treatment is presently to assess HER2/neu overexpression along with other biomarkers for targeted treatments.[5] HER2/neu oncogene overexpression and amplification has emerged as a critical indicator for determining patient's response to HER2/neu targeted therapy.

There has been some evidence that Ki-67 can be correlated with outcome in stomach cancer.[6]

This study aimed to investigate the clinicopathological spectrum of gastric cancer, and to assess HER2/neu and the Ki-67 index using immunohistochemistry (IHC) techniques on diagnosed cases of adenocarcinoma. This study tried to find correlation of HER2/neu expression and the Ki-67 index with various histomorphological variations and grade of gastric adenocarcinoma.

This study was undertaken to diagnose the cases of gastric adenocarcinoma by histopathology, determine its incidence, and study the prevalence of HER2/neu expression and Ki-67 index according to location, histopathological types, grading, and staging. The correlation between HER2/neu and Ki-67 was also determined.

Objectives

The objectives were to study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma and to determine the correlation between HER2/neu expression and Ki-67 index.

[a] An online database providing global cancer statistics and estimates of incidence and mortality in 185 countries for 36 types of cancer, and for all cancer sites combined.

Materials and Methods

Study Design

This is a prospective study done in a tertiary care hospital, Kolkata, West Bengal from January 2019 to June 2020.

Primary Outcome

To study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma.

Secondary Outcome

To study the correlation between HER2/neu expression and Ki-67 index.

Inclusion Criteria

Patients clinically diagnosed with gastric adenocarcinoma and who underwent gastric endoscopic biopsy or gastrectomy for the same.

Exclusion Criteria

Patients with a history of gastric adenocarcinoma, treated with chemotherapy and gastric cancer cases diagnosed other than gastric adenocarcinoma were excluded. Detailed history, clinical features, and radiological investigation were evaluated.

The specimens were processed for histopathological and immunohistochemical study. Hematoxylin and eosin stain was used to stain the sections for histopathological study and cases diagnosed as gastric adenocarcinoma were evaluated for immunohistochemical study with HER2/neu and Ki-67.

The three authors independently scored HER2/neu IHC using the Gastric Cancer Scoring System for surgical specimens.[7] The cases were examined with standard HER2/neu positive criteria. Brown staining of malignant cell membrane was used to assess positivity. A score of 3+ was considered positive for HER2/neu.

HER2 IHC Pattern in Surgical Specimen

Score 0 negative: No reactivity or membranous reactivity in $<$10% of cancer cells.
Score 1+ negative: Faint or barely perceptible membranous reactivity in $\geq$10% of cancer cells; cells are reactive only in part of their membrane.
Score 2+ equivocal: Weak to moderate complete, basolateral or lateral membranous reactivity in $\geq$10% of tumor cells.
Score 3+ positive: Strong complete, basolateral or lateral membranous reactivity in $\geq$10% of cancer cells.

HER2 IHC Pattern in Biopsy Specimen

Score 0 negative: No reactivity or no membranous reactivity in any cancer cell.
Score 1+ negative: Cancer cell cluster[b] with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive.
Score 2+ equivocal: Cancer cell cluster[b] with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive.

[b] Cancer cell cluster consisting of $\geq$5 neoplastic cells

Score 3+ positive: Cancer cell cluster[b] with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive.

Ki-67 IHC scoring was performed in accordance with the International Ki-67 in Breast Cancer Working Group[8] criteria, with Ki-67 positive staining defined as positive nuclear staining only, irrespective of intensity of staining. At least 1,000 nuclei counted at high power (×40 objective) was required for scoring.

The Ki-67 score/index or proliferation index was calculated as percentage of positively stained nuclei in the area scored out of total number of nuclei.

Cases were then divided into two groups for suitable grouping of results: GCs having high Ki-67 score (>20%) and GCs having low Ki-67 score (≤20%).

Statistical Analysis

Available data were statistically evaluated with SPSS (version 21.0, IBM, Chicago, Illinois, United States) for windows software.

Ethics

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 Declaration of Helsinki and its later amendments or comparable ethical standards. We began our research only after receiving approval from the ethical committee. This work has been approved by our institution's proper ethical committee. Ethical approval number is EC-CNMC/2019/220, date January 11, 2019, Institutional Ethics Committee, Calcutta National Medical College.

Results

In our study, the patient's mean age was 59.1 ± 10.9 years, having a range from 32 to 83 years, with male preponderance (3:1). We studied 38 (70%) specimens of gastrectomy, whereas gastric biopsies account 16 (30%) cases. Antrum (48.15%) was the most frequent location followed by pylorus (24.07%).

Intestinal variant was higher (87.04%) than the diffuse variant and majority of gastric adenocarcinoma cases were moderately differentiated (grade 2) (62.96%) (►**Fig. 1**), followed by poorly differentiated (grade 3) (27.78%) and few cases were well differentiated (grade 1) (9.26%).

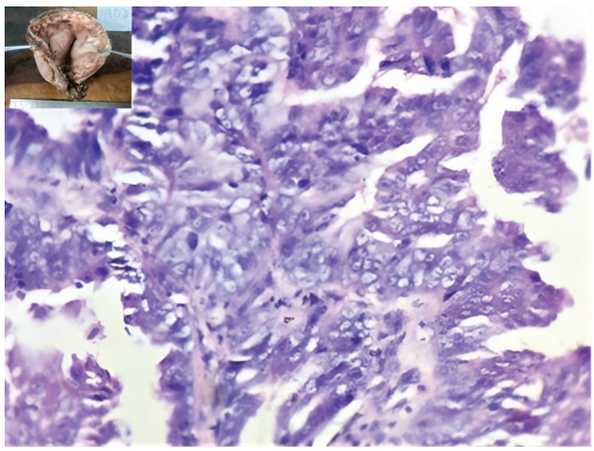

Fig. 1 Moderately differentiated gastric adenocarcinoma; hematoxylin and eosin stain ×40 and inset showing gross specimen of radical gastrectomy showing diffuse infiltrative growth involving whole of the specimen.

Table 1 Clinicopathological characteristics of patients

Characteristics	Number of patients ($n = 54$) (%)
Age	
Range	32–83
Mean	59.1 ± 10.9
Sex	
Male	40 (74.07)
Female	14 (25.93)
Type of specimen	
Gastrectomy	38 (70.37)
Gastric biopsy	16 (29.63)
Location of tumor	
GE junction	2 (3.7)
Fundus	1 (1.85)
Body	9 (16.67)
Incisura	3 (5.56)
Antrum	26 (48.15)
Pylorus	13 (24.07)
Lauren's classification	
Intestinal	47 (87.04)
Diffuse	7 (12.96)
Grade of tumor	
Well differentiated	5 (9.26)
Moderately differentiated	34 (62.96)
Poorly differentiated	15 (27.78)
Pathological tumor stage	
T1	16 (29.63)
T2	5 (9.26)
T3	25 (46.30)
T4	8 (14.81)
Pathological nodal stage	
Nx	16 (29.63)
N0	6 (11.11)
N1	6 (11.11)
N2	16 (29.63)
N3	10 (18.52)

Table 1 (*Continued*)

Characteristics	Number of patients ($n = 54$) (%)
TNM stage	
I	3 (7.90)
II	10 (26.32)
III	25 (65.78)
IV	0 (0)
HER2/neu score	
0	19 (35)
1+	6 (11)
2+	14 (26)
3+	15 (28)
Ki-67 proliferation index	
High	22 (40.75)
Low	32 (59.25)

Abbreviations: GE, gastroesophageal; HER2, human epidermal growth factor receptor 2.

The majority of gastrectomy patients (65.78%) had stage III disease according to TNM staging (►**Table 1**).

In this study, including 54 cases of gastric adenocarcinoma, 15 cases (28%) were positive for HER2/neu (►**Fig. 2**). HER2/neu expression was more prevalent in adenocarcinoma of distal part of stomach, antrum (38%), pylorus (30%) which is statistically significant ($p = 0.02$). Out of the 15 HER2/neu positive cases, there were 14 intestinal variant cases and only 1 was diffuse variant case.

Adenocarcinoma with moderate differentiation (grade 2) displayed highest HER2/neu positivity (score 3 +) (►**Fig. 3**) followed by poor differentiation (grade 3).

No significant association ($p = 0.06$) was noted among positive expression of HER2/neu and pathological tumor (pT) stage, but a statistically significant association ($p = 0.009$) noted among positive expression of HER2/neu and pathological nodal (pN) stage (►**Table 2**).

In our study of 54 cases, 40.75% cases had high Ki-67 proliferation index (►**Fig. 4**), out of which 62% had T4 stage gastric adenocarcinoma cases showing high Ki-67 score.

A significant correlation was noted between Ki-67 index and site of gastric adenocarcinoma ($p = 0.05$).

The diffuse type (57%) had high Ki-67 score and poorly differentiated adenocarcinoma (53%) had high Ki-67 score (►**Fig. 5**).

A statistically significant correlation was noted between Ki-67 score and pN stage ($p = 0.002$). pN3 gastric adenocarcinoma (90%) cases showed high Ki-67 score (►**Table 3**).

Thirteen out of total 15 HER2/neu positive cases had high Ki-67 score. A positive correlation was noted HER2/neu score and Ki-67 score ($p = 0.007$) (correlation coefficient = 0.4) (►**Table 4**).

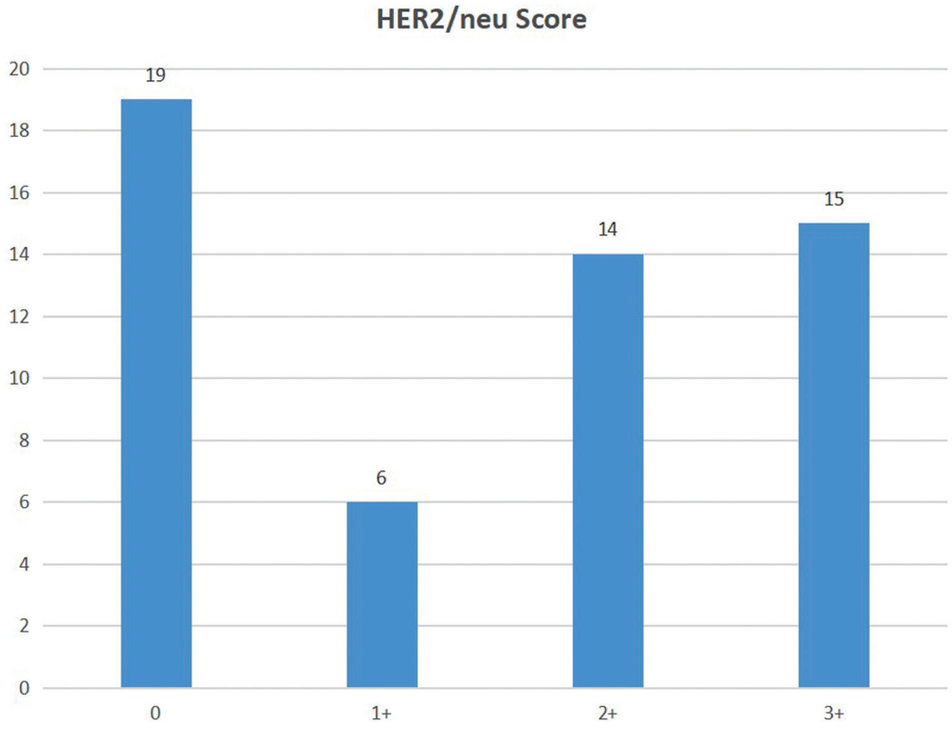

Fig. 2 Bar diagram showing distribution of gastric adenocarcinoma cases according to HER2/neu score. HER2, human epidermal growth factor receptor 2.

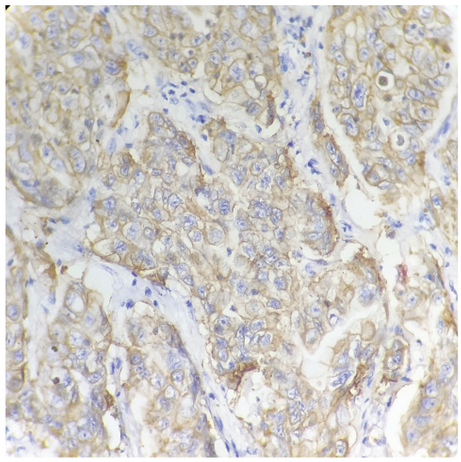

Fig. 3 Moderately differentiated gastric adenocarcinoma showing positive membranous staining for HER2/neu; immunohistochemistry ×40. HER2, human epidermal growth factor receptor 2.

Discussion

A study conducted by Amrani et al[9] and Ahadi et al[10] which was similar to our study also showed that patient's mean age was 59.1 ± 10.9 years, with male preponderance (3:1).

In our study, antrum (48.15%) was the most frequent location followed by pylorus (24.07%) similar to Aditi et al[11] and Mohapatra et al's study.[12]

Intestinal subtype was more common (87.04%) than the diffuse subtype in our study, similar to the study of Shah et al (2019)[13] and Shabbir et al (2018).[14]

Raj et al's[15] study also similarly showed that majority of gastric adenocarcinoma cases were moderately

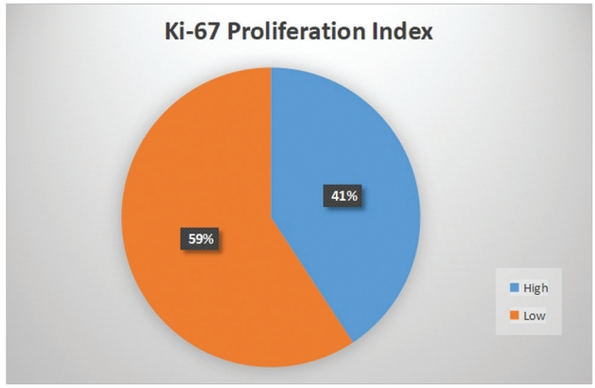

Fig. 4 Pie chart showing distribution of gastric adenocarcinoma cases according to Ki-67 proliferation index.

Table 2 Association between HER2/neu of the patients with different clinicopathological parameters

Clinicopathological parameters	HER2/neu score				p-Value
	0	1+	2+	3+	
Site					
Proximal (GE junction, incisura, fundus, body) ($n = 15$)	7	0	7	1	0.02
Distal (antrum, pylorus) ($n = 39$)	12	6	7	14	
Type					
Intestinal ($n = 47$)	18	5	10	14	0.23
Diffuse ($n = 7$)	1	1	4	1	
Grade					
Well differentiated (grade 1) ($n = 5$)	3	2	0	0	0.09
Moderately differentiated (grade 2) ($n = 34$)	12	2	8	12	
Poorly differentiated (grade 3) ($n = 15$)	4	2	6	3	
Pathological tumor stage					
T1 ($n = 16$)	9	2	5	0	0.06
T2 ($n = 5$)	3	2	0	0	
T3 ($n = 25$)	7	1	7	10	
T4 ($n = 8$)	0	1	2	5	
Pathological nodal stage					
Nx ($n = 16$)	9	2	5	0	0.009
N0 ($n = 6$)	5	1	0	0	
N1 ($n = 6$)	2	1	3	0	
N2 ($n = 16$)	3	1	4	8	
N3 ($n = 10$)	0	1	2	7	

Abbreviations: GE, gastroesophageal; HER2, human epidermal growth factor receptor 2.

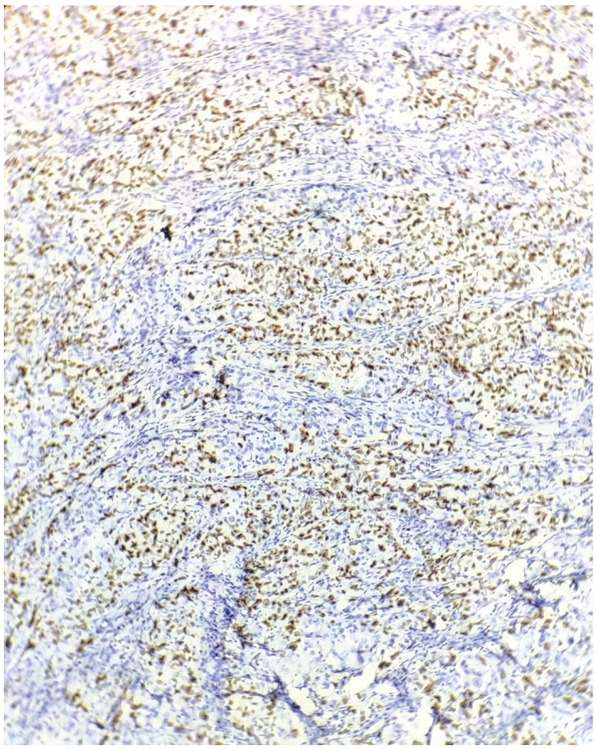

Fig. 5 Poorly differentiated gastric adenocarcinoma showing score 3+ positive nuclear staining for Ki-67 marker; immunohistochemistry ×10.

differentiated (grade 2) (62.96%), followed by poorly differentiated (grade 3) cases (27.78%) and least cases were well differentiated (grade 1) (9.26%).

In our study, most of the gastrectomy patients (65.78%) had stage III disease which was comparable to the research conducted by Aditi et al (2016)[11] and Pramanik et al[16] where out of 17 resection specimens, 10 had (58.8%) stage III disease and majority (71.1%) had stages III and IV disease, respectively.

Among 54 cases, HER2/neu positivity was expressed by 15 (28%) cases which was comparable to the research done by Aditi et al (2016),[11] Ghosh et al (2016),[17] and Pramanik et al (2020).[16]

HER2/neu expression was more prevalent in adenocarcinoma of distal part of stomach, antrum (38%), pylorus (30%) which was found to be statistically significant ($p = 0.02$) and concordant with the findings of the study by Mohapatra et al (2020).[12]

Among 15 HER2/neu positive cases, there were 14 intestinal cases and only one diffuse case which is consistent with the research of Dawa and Zedan (2018),[18] Ghosh et al (2016),[17] and Aditi et al (2016).[11]

Adenocarcinoma with moderate differentiation (grade 2) displayed highest HER2/neu positivity (score 3+) followed by poor differentiation (grade 3).

Similar findings also were seen in the study by Raj et al (2018)[15] and Shah et al (2019)[13].

Our study showed no significant correlation between positive HER2/neu score and pT stage ($p = 0.06$) as also shown in the research by Ahadi et al (2020)[10] and Pramanik et al (2020).[16]

But a statistically significant correlation was seen between HER2/neu positivity and pathologic T-stage ($p = 0.026$) in the study by El-Gendi et al (2015).[19]

A statistically significant association was noted among HER2/neu positivity and pN stage ($p = 0.009$) similarly as in the research by Mohapatra et al (2020).[12]

In our study, 40.75% of the 54 patients had Ki-67 proliferation index comparable to the research by Ahadi et al (2020) [10] where 33.75% patients had high Ki-67 proliferation index.

Low Ki-67 index tumors were more proximally located, similar to the study findings by Fradique et al.[20].

The Ki-67 index showed significant association with gastric adenocarcinoma site in our study ($p = 0.05$).

The diffuse gastric adenocarcinoma (57% cases) showed high Ki-67 score which was similar with the study by Pramanik et al (2020).[16]

In our study, 53% of poorly differentiated adenocarcinoma (grade 3) showed high Ki-67 proliferative index which was consistent with the study by Lazăr et al (2010).[21]

In our study, 62% of T4 stage gastric adenocarcinoma cases showed high Ki-67 index which was in concordance with the findings done by El-Gendi et al (2015).[19]

In our study, 90% of pN3 gastric adenocarcinoma cases showed high Ki-67 index which had statistical significance ($p = 0.002$), whereas for pN2 and pN3 carcinomas, Lazăr et al's study (2010)[21] noted "high Ki-67 scores in only 39.1 and 25% of cases."

Our study showed 13 out of 15 HER2/neu positive cases with high Ki-67 score, and positive correlation was noted between HER2/neu score and Ki-67 index ($p = 0.007$) (correlation coefficient = 0.4) which is consistent with the study of Ahmed and Al-Tamimi (2018)[22] where "high Ki-67 index was significantly significant, p-value <0.01 in HER2/neu positive cases."

Conclusion

To conclude, our study showed out of 54 cases of gastric adenocarcinoma, there were predominantly males of age 59.1 ± 10.9 years. Most of the gastric adenocarcinoma cases present on antrum and were moderately differentiated, stage III intestinal type.

HER2/neu overexpression was found in 28.0% cases which was statistically significant and correlated with location ($p = 0.02$), pN stage ($p = 0.009$) of the tumor.

High Ki-67 index expression were shown in 40.75% cases of gastric adenocarcinoma. Out of which majority were poorly differentiated, stage III diffuse type. There was a significant correlation between Ki-67 index with location of tumor ($p = 0.05$) and pN stage ($p = 0.002$).

Positive HER2/neu and high Ki-67 index had association with higher pT stage and pN stage evidencing an aggressive behavior.

Our study supports the view that patients with HER2/neu positivity and high Ki-67 index have poorer prognosis.

Positive HER2/neu cases (87%) showed high Ki-67 score and a positive correlation noted between HER2/neu score and Ki-67 score ($p = 0.007$) (correlation coefficient = 0.4).

Table 3 Association between Ki-67 index of the patients with different clinicopathological parameters

Clinicopathological parameters	Ki-67 index		*p*-Value
	Low	High	
Site			
Proximal (GE junction, incisura, fundus, body) ($n=15$)	12	3	0.05
Distal (antrum, pylorus) ($n=39$)	20	19	
Type			
Intestinal ($n=47$)	29	18	0.34
Diffuse ($n=7$)	3	4	
Grade			
Well differentiated (grade 1) ($n=5$)	4	1	0.37
Moderately differentiated (grade 2) ($n=34$)	21	13	
Poorly differentiated (grade 3) ($n=15$)	7	8	
Pathological tumor stage			
T1 ($n=16$)	12	4	0.19
T2 ($n=5$)	4	1	
T3 ($n=25$)	13	12	
T4 ($n=8$)	3	5	
Pathological nodal stage			
Nx ($n=16$)	12	4	0.002
N0 ($n=6$)	6	0	
N1 ($n=6$)	5	1	
N2 ($n=16$)	8	8	
N3 ($n=10$)	1	9	

Abbreviation: GE, gastroesophageal.

Table 4 Correlation between HER2/neu scoring and Ki-67 index in gastric adenocarcinoma

HER2/neu score	Ki-67 +ve	Ki-67 −ve
HER2/neu +ve ($n=15$)	13 (87%)	2 (13%)
HER2/neu −ve ($n=39$)	9 (23%)	30 (27%)
Total ($n=54$)	22 (41%)	32 (59%)

Abbreviation: HER2, human epidermal growth factor receptor 2.

Though unavailability of fluorescence in situ hybridization for equivocal HER2/neu cases and follow-up of all the patients could not be assessed; however, immunohistochemical assessment of the HER2/neu score and Ki-67 score in our study appeared to be useful in detecting prognostic correlation in patients with advanced adenocarcinomas.

Our study can help clinicians to optimize the management of gastric adenocarcinoma patients by choosing candidates for trastuzumab-based therapy and may help improve understanding of the therapy's efficacy in HER2/neu positive gastric cancers.

Funding
None declared.

Conflict of Interest
None declared.

Acknowledgments
The corresponding author's profound appreciation goes to all the coauthors for their invaluable guidance, constant encouragement, and supervision toward the completion of this research work. The corresponding author acknowledge that this research would not have been feasible without the participation of all the patients in the trial.

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Systemic Immune-Inflammation Index Predicts Outcomes in Platinum-Resistant Relapsed Ovarian Cancer

Luxitaa Goenka[1] Nakka Thejeswar[1] Biswajit Dubashi[1] Smita Kayal[1] Prasanth Ganesan[1]

[1] Department of Medical Oncology, JIPMER, Puducherry, India

Ind J Med Paediatr Oncol 2024;45:430–433.

Address for correspondence Prasanth Ganesan, MD, DM, Department of Medical Oncology, JIPMER, Dhanvantri Nagar, Puducherry 605006, India
(e-mail: p.ganesan@jipmer.edu.in; pg1980@gmail.com).

Abstract

We explored the prognostic impact of simple indices that reflect the immunological milieu (neutrophils to lymphocyte ratio [NLR] and systemic immune-inflammation [SII]) in 49 platinum-resistant relapsed ovarian cancer patients. The median progression-free survival (PFS) and overall survival (OS) were 4 and 8 months, respectively. Patients with a lower NLR ($\leq$2.89) had a better PFS (5 vs. 2 months [$p = 0.02$]) and OS (9 vs. 5 months [$p = 0.20$]). Factors associated with a worse PFS were NLR > 2.8 (hazard ratio [HR] =2.32, $p = 0.02$) and SII > 639 (HR =3.70, $p = 0.002$). SII > 639 independently predicted PFS (HR =4.13, $p = 0.03$). Future studies should study the validity of inflammatory markers and could consider incorporating it as a biomarker in clinical trials.

Keywords

- platinum-resistant ovarian cancer
- treatment
- outcomes
- systemic immune-inflammation indices
- neutrophil to lymphocyte ratio

Majority (70–80%) of the epithelial ovarian cancers (EOC) recur with current therapy.[1] Patients who progress within 6 months of platinum-based chemotherapy are considered to have platinum-resistant ovarian cancer (PROC) disease and have a very poor prognosis. The median progression-free survival (PFS) in PROC is 3 to 4 months, and the median overall survival (OS) is 1 year.[2] Other than "platinum-refractory disease" (progression during or within 4 weeks of platinum-based therapy [median OS: 3–5 months]), few factors have been consistently associated with prognosis in PROC. We explored the prognostic impact of simple indices that reflect the immunological milieu (neutrophils to lymphocyte ratio [NLR] and systemic immune-inflammation [SII]) in patients with PROC. Inflammatory indices are prognostic in ovarian cancer (newly diagnosed and platinum-sensitive recurrence), but there are no reports in patients with PROC.[3,4] After obtaining approval from the Institutional Ethics Committee (EC Approval No: JIP/IEC/2019/558), data of patients diagnosed with PROC between January 1, 2015 and December 31, 2019 was collected. The diagnosis of relapse could be based on the elevation of CA-125 or symptoms/imaging findings. PFS was defined from the start of treatment of PROC until progression or death due to any cause. SII (platelet count $\times$ neutrophil count)/lymphocyte count and NLR (absolute neutrophil count/absolute lymphocyte count) were calculated. Their median values were used to divide patients into high and low categories.

Forty-nine patients who had started treatment for PROC ($n = 21$ with "refractory" disease) were included in this analysis (►**Fig. 1**). The median interval between the last platinum treatment to relapse was 3.2 (2.1–4.6) months. All had undergone surgery during initial treatment, either upfront ($n = 9$, 18%) or interval ($n = 40$, 82%). At the time of diagnosis of PROC, 19 (39%) patients were symptomatic, 2 (4%) had isolated elevation of CA-125, and 28 (57%) had elevated CA-125 with abnormal imaging. For resistant disease, the majority received only chemotherapy ($n = 45$ [91%]), while few underwent additional surgery ($n = 4$[8%]).

article published online
July 28, 2022

DOI https://doi.org/10.1055/s-0042-1749399.
ISSN 0971-5851.

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

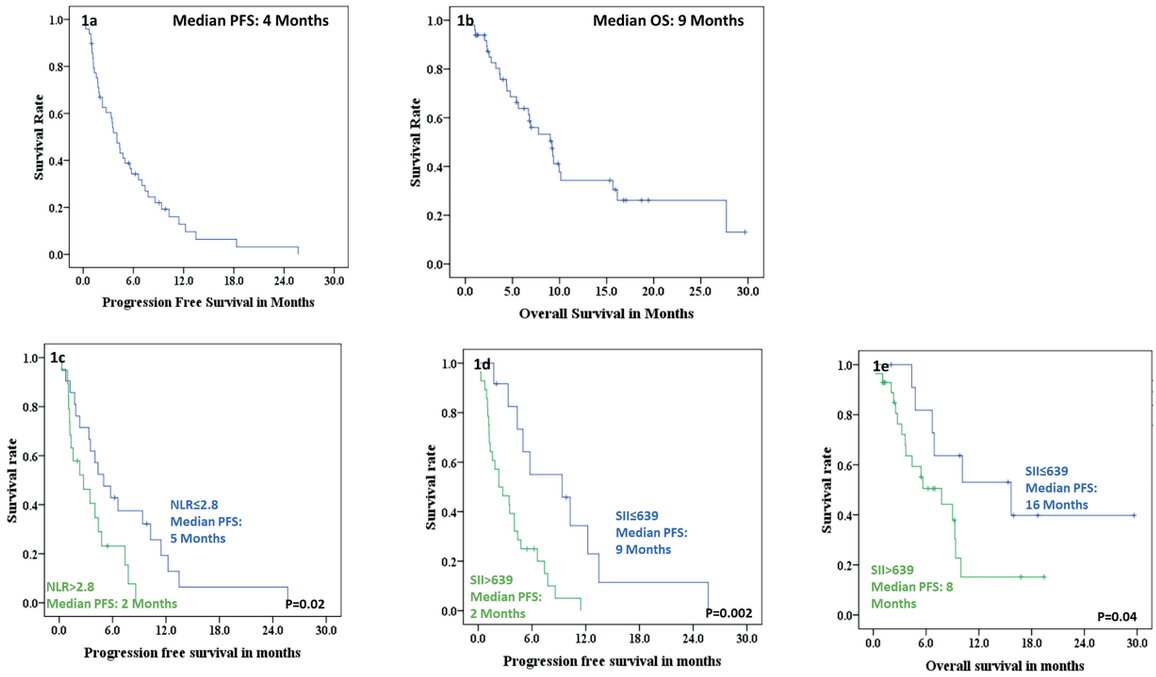

Fig. 1 The Kaplan–Meier analysis of progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) in patients with platinum-resistant ovarian cancer (PROC). Factors affecting survival in patients with PROC. Comparison of PFS between patients with high and low neutrophils to lymphocyte ratio (NLR) (**C**) and systemic immune-inflammation index (SII) (**D**). Comparison of the OS between patients with high and low SII (**E**).

Most received single-agent chemotherapy ($n = 27$), while a few received doublets ($n = 22$). The median number of chemotherapy cycles was 4 (range: 2–6). The overall response rate (ORR) was 21%. After a median follow-up of 3 (range: 2–7) months, 33 (67%) patients progressed, and 25 (57%) had died. During secondary progression, 25 patients (76%) were symptomatic, 4 (12%) had an elevation of CA-125, and 4 (12%) had both elevations of CA-125 and radiological imaging (►**Supplementary Table S1** [online only]).

The median PFS and OS were 4 (95% confidence interval [CI]: 2.44–4.55) and 9 months (95% CI: 4.77–10.76), respectively (►**Fig. 1A** and **1B**). Patients with a lower NLR (≤2.89) had a better PFS (5 vs. 2 months [$p = 0.02$]) and OS (9 vs. 5 months [$p = 0.20$]) when compared with patients with higher NLR (>2.89) (►**Fig. 1C**). Patients with lower SII≤639 had a better PFS (9 vs. 2 months [$p = 0.002$]) and OS (16 vs. 8 months [$p = 0.04$]) in comparison to patients with higher SII (►**Fig. 1D** and **1E**). On univariate analysis, the following factors were associated with a worse PFS: NLR > 2.8 (hazard ratio [HR] =2.32, $p = 0.02$) and SII > 639 (HR =3.70, $p = 0.002$) (►**Table 1**). On multivariate analysis (including NLR and SII), SII > 639 was the only factor that predicted survival (HR =4.13, $p = 0.03$) for PFS.

Even though PROC has a poor prognosis, this group has recognized heterogeneity.[5] Identifying patients with PROC who may benefit from subsequent therapy is currently based on clinical judgment (performance status, rapidity of progression, number of previous lines, and patient wish to continue potentially toxic treatment with a low expectation of benefit). There is a need for more objective markers to determine prognoses. This may help us tailor more intense therapies and stratify patients included in clinical trials in this segment. This is one of the first studies looking at the impact of inflammatory indices in PROC. We demonstrated that SII calculated at the time of diagnosis of PROC is a powerful independent predictor of outcomes (HR of 4.1 for PFS) among patients with PROC undergoing second/third line of chemotherapy.

Systemic inflammation induced by cancer cells may aid tumor progression by several mechanisms.[6] These indices have also been identified as powerful independent prognostic factors in various cancers. In patients with newly diagnosed EOC, SII, NLR, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio have been shown to predict outcomes. Recently, predictive abilities have been demonstrated in patients with platinum-sensitive relapsed ovarian cancer.[3,7] Neutrophil infiltration of the tumor is associated with tumor growth (release of proinvasive factors, angiogenesis)[8] while less amount of CD8+ tumor-infiltrating lymphocytes is associated with poorer prognosis.[9,10] Thus, the combination of high neutrophil and low lymphocytes in the peripheral blood reflects an immunological milieu that favors tumor growth which explains the predictive ability of the SII. Earlier studies have also demonstrated that SII could predict therapeutic benefit.[3] Patients with higher SII (≥730) levels did not show any benefit with the addition of bevacizumab to chemotherapy (when compared with those with lower SII who benefited from the addition of bevacizumab).

Other studies attempting to develop prognostic nomograms in PROC have not incorporated SII in their models.[11,12] Also, there is a paucity of real-world studies on PROC; most

Table 1 Univariate analysis of survival outcomes in platinum resistant/refractory patients

Variable	*n*	Median PFS	95% CI	HR	*p*-Value	Median OS	95% CI	HR	*p*-Value
Duration from last platinum									
3–6 mo	28	4	1.47–6.59	1	0.88	9	6.67–12.05	1	0.59
< 3 mo	21	3	1.19–6.00	1.04		6	0.00–13.41	1.22	
ECOG[a]									
0,1	13	9	0.00–13.64	1	0.10	27	0.00–63.14	1	0.04
2,3	24	3	2.23–4.88	2.01		7	2.60–10.79	2.93	
Type of therapy for PROC[b]									
IV chemotherapy doublet									
Yes	22	4	1.57–5.36	1	0.60	5	8.49–11.73	1	0.08
No	27	5	2.39–7.60	0.85		9	3.55–7.31	0.52	
IV chemotherapy single agent									
Yes	5	4	0.00–11.45	1	0.63	4	0.00–9.37	1	0.40
No	44	4	2.86–5.19	1.29		9	7.31–11.24	1.59	
Oral etoposide									
Yes	22	6	2.22–8.97	1	0.82	10	3.23–8.02	1	0.02
No	27	4	1.93–6.13	1.07		5	8.75–9.78	2.31	
Number of previous lines of treatment									
1	38	4	2.40–4.95	1	0.96	7	3.95–9.91	1	0.69
2	11	4	3.61–5.18	1.02		6	3.86–9.73	1.25	
NLR									
≤2.8	19	5	2.40–7.59	1	0.02	10	6.11–13.81	1	0.11
> 2.8	21	2	0.23–5.23	2.32		5	0.95–9.90	1.94	
SII									
≤639	12	9	2.94–15.79	1	0.002	16	3.95–27.38	1	0.04
> 639	28	2	0.22–4.37	3.70		8	3.25–12.27	2.49	
LMR									
> 6.7	20	4	2.24–6.48	1	0.09	9	6.45–12.08	1	0.75
≤6.7	20	2	0.12–5.51	1.77		7	2.62–11.24	1.13	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival; SII, systemic immune-inflammation index; HR, hazard ratio.
[a]At the time of platinum resistance.
[b]The chemotherapy regimens used were paclitaxel/carboplatin ($n = 7$, 14%), lipodox/carbo ($n = 4$, 8%), single-agent lipodox ($n = 5$, 10%), oral etoposide ($n = 22$, 45%), and gemcitabine/epirubicin/carbo ($n = 11$, 22%).

data are from trials or analysis of specific treatments such as bevacizumab or oral metronomic chemotherapy. Although this study is limited by the small sample size and its retrospective nature, ours is the first data showing that SII could be a useful prognostic predictor in patients with platinum-refractory/resistant disease. The treatment undergone by the patients was uniform—all our patients received chemotherapy, and there were no patients treated with bevacizumab or other targeted agents. Though several studies in different types of cancers have shown the usefulness of this index, it is yet to be incorporated into practice. Future studies should study the validity of inflammatory markers in PROC and could consider incorporating it as a biomarker in clinical trials.

Ethical Approval

The study was approved by JIPMER IEC (EC Approval No: JIP/IEC/2019/558).

Funding

The study was supported by JIPMER. No grant number is applicable.

Conflicts of Interest/Disclosure

None of the authors have any relevant conflicts of interest to declare.

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Upfront Low-Dose Cytarabine with Prednisolone for Langerhans Cell Histiocytosis with Liver Dysfunction: A Ray of Hope

Niranjan Gurunath Hegde[1] Meena S. Sivasankaran[1] Vimal Kumar G.[2] Deenadayalan Munirathnam[2]

[1] Department of Pediatric Hemato-Oncology and BMT, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu, India
[2] Department of Pediatric Hemato-Oncology, Immunology and Stem cell transplantation, Dr Rela Institute and Medical Centre, Chennai, Tamil Nadu, India

Address for correspondence Niranjan Gurunath Hegde, FIAP (PHO), DNB (Pediatrics), Department of Pediatric Hematology Oncology and BMT, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu, India (e-mail: gh.niranjana@gmail.com).

Ind J Med Paediatr Oncol 2024;45:434–438.

Abstract

The management of Langerhans cell histiocytosis (LCH) with accompanying liver dysfunction poses significant challenges, and this prompted the development of a modified low-dose cytarabine and prednisolone regimen. In this prospective observational study on children with LCH and liver dysfunction, four patients underwent induction and maintenance chemotherapy. The induction phase included 5 days of 100 mg/m^2 cytarabine and 4 weeks of 40 mg/m^2 daily prednisolone, with subsequent tapering. Maintenance included a regimen of 5 days of 100 mg/m^2 cytarabine, along with oral prednisolone, repeated every 3 weeks. Complete disease resolution occurred after varying chemotherapy cycles. Three patients had liver transplants, and the chemotherapy resumed for 52 weeks after the transplant. In one child, chemotherapy was continued after reaching remission. In conclusion, a modified, less toxic low-dose cytarabine-based chemotherapy effectively managed LCH with liver dysfunction, with liver transplantation as a postremission treatment option.

Keywords
- decompensated liver
- PET-CT
- sclerosing cholangitis
- liver transplantation

Introduction

Langerhans cell histiocytosis (LCH) is characterized by aggressive proliferation of histiocytes causing tissue destruction at the involved sites. The liver is affected in 20 to 60% of patients with LCH and is more common when there is multiorgan involvement.[1] A prototype hepatic LCH is secondary sclerosing cholangitis (SSC), which is caused by progressive destruction of the biliary tree by malignant histiocytes.[1] It is one of the "risk organs," apart from the spleen and bone marrow, as this can adversely affect long-term survival. Liver involvement is divided into two stages: the infiltrative phase (early) and the sclerosis phase (late). In the early infiltrative phase, inflammatory mediators/cells infiltrate the periportal area in response to malignant histiocytes. Nodular lesions were observed during this phase. In the late sclerosing phase, the liver develops scarring and cirrhosis, leading to portal hypertension.[2,3]

Chemotherapy remains the mainstay of treatment.[4] Vinblastine plus prednisone has been the standard of care for children with multisystem disease. Although overall survival has steadily improved, outcomes for patients with LCH with liver dysfunction remain suboptimal.[5] It is advisable to refrain from administering vinblastine in the presence of liver dysfunction to mitigate the risk of toxicity.[6,7] Therefore, there is a pressing need for an alternative treatment regimen. Limited research exists on the use of cytarabine as an initial therapy and as an alternative regimen in children with liver dysfunction. In the present study, we evaluated the

article published online
May 23, 2024

DOI https://doi.org/10.1055/s-0044-1782234.
ISSN 0971-5851.

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

effectiveness of a low-dose cytarabine/prednisolone-based therapy in terms of treatment response and associated toxicity.

Definitions

Liver involvement in LCH was defined as per the European Consortium for Histiocytosis as palpable liver 3 cm below the costal margin along the mid-clavicular line, and liver dysfunction defined by hyperbilirubinemia (at least three times the upper limit of normal), hypoalbuminemia (<3.0 g/dL), elevated alanine transaminase (ALT), and/or aspartate transaminase (AST; more than three times the upper limit of normal), elevated gamma glutamyl transpeptidase (GGT; more than twice the upper limit of normal), ascites, and/or intrahepatic nodular mass.[8] Decompensated liver disease is defined as ascites, variceal bleed or Hepatic Encephalopathy (HE), and bilirubin >3 mg/dL, and/or acute on chronic liver failure (acute on chronic liver failure is bilirubin more than 5 mg/dL with international normalized ratio [INR] above 1.5 along with onset of ascites and/or HE within 4 weeks of onset of jaundice).[4,9] Sclerosing cholangitis in LCH is defined as involvement of extrahepatic or intrahepatic biliary tree with strictures, dilatation, abnormal branching detected on imaging (computed tomography or magnetic resonance imaging), and/or on liver biopsy with or without elevated GGT.[10] The treatment response is defined as per the LCH-IV study, namely, no active disease (NAD), active disease (AD) better, intermediate, and worse.[11]

Materials and Methods

Chemotherapy Protocol

Children in our study received modified low-dose cytarabine-based chemotherapy.[12–14] The induction regimen included cytarabine administered at a dosage of 100 mg/m^2 per day. The administration was carried out either through intravenous infusion over 1 hour or via subcutaneous delivery. The treatment spanned 5 consecutive days every 3 weeks. This was combined with daily prednisolone at a dose of 40 mg/m^2 for 4 weeks, followed by gradual tapering over the subsequent 2 weeks. Subsequently, the treatment response was assessed at 6 and 12 weeks. Induction chemotherapy was continued until complete remission or 12 weeks, whichever was earlier, as long as there was no progression of the disease. After induction, maintenance chemotherapy commenced. It involved three weekly doses of cytarabine at a dose of 100 mg/m^2 for 5 days, along with prednisolone at 40 mg/m^2/d for 5 days. Likewise, the total duration of treatment spanned 52 weeks (►**Fig. 1**).

This was a prospective observational study conducted in a tertiary care hospital in Chennai. The study was conducted over 5 years (2018–2022). Children with biopsy-proven LCH and decompensated liver disease were included in this study. Children who had received chemotherapy prior to the study were excluded. We had four children in the cohort. Demographic data, growth parameters, and essential blood investigations (i.e., complete blood count and liver function test, and positron emission tomography and computed tomography [PET-CT] at diagnosis and subsequently during response

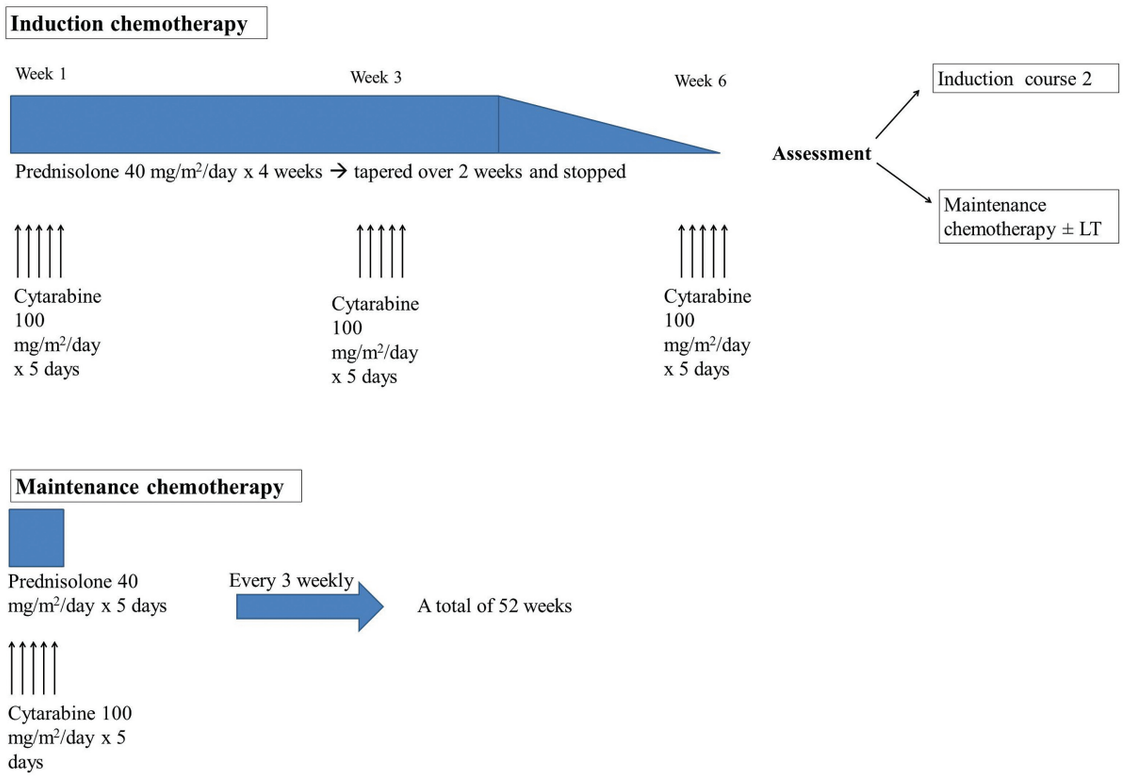

Fig. 1 Chemotherapy protocol: modified low-dose cytarabine-prednisolone-based chemotherapy.

assessment) were tabulated. Chemotherapy was administered as described above. If the disease showed complete remission at the end of 6 weeks, either the child was taken up for liver transplantation or continued on further maintenance chemotherapy to complete 52 weeks. If there was an intermediate or better response at the end of 6 weeks, chemotherapy was administered for 6 more weeks. Response was reassessed using PET-CT at the end of 12 weeks of chemotherapy. Children were continued on induction chemotherapy until complete remission or 12 weeks, whichever was earlier. If disease progression occurred at any point during induction, a salvage chemotherapy regimen was initiated.

Liver transplantation was performed in patients with acute decompensation or in children with compensated cirrhosis and sclerosing cholangitis with portal hypertension, intractable pruritus, and growth retardation.

Results

All four patients showed favorable response (NAD, AD better, or AD intermediate) to chemotherapy. Complete resolution (NAD) of the disease was attained at the end of two cycles in patients 1 and 4, whereas patients 2 and 3 attained complete resolution at the end of 13 and 5 cycles, respectively. Three patients with persistent liver dysfunction underwent liver

Table 1 Patient characteristics, evaluation, treatment received, and outcomes

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Male	Male	Male
Age at symptom onset (mo)	36	6	20	8
Age at diagnosis (mo)	48	11	23	12
Hb (g/dL)	8.9	8.5	9.4	6
TLC (cells/mm^3)	18,220	15,240	19,800	23,900
Platelets (lakhs/mm^3)	5.2	4.1	6.21	11.47
PET-CT	Metabolically active liver, periportal and thoracic lymph nodes	Metabolically active middle ear cavity, mastoid air cells, bilateral level II, III, IV cervical lymph nodes, bilateral lungs, liver, spleen, and left femur	Metabolically active left temporal, petrous, orbit, sphenoid, liver, and bone marrow	Metabolically active liver, lungs, mediastinum, LNs, and bone marrow
Chemotherapeutic agents	Prednisolone, cytarabine	Prednisolone, cytarabine	Prednisolone, cytarabine	Prednisolone, cytarabine, trametinib
Post-chemo PET-CT (2 cycles/6 wk)	NAD	Intermediate response overall	AD better	Intermediate response in mediastinum; NAD elsewhere
Post-chemo PET-CT (4 cycles/12 weeks; if relevant)		Intermediate response in the lungs; AD better in liver, LNs; NAD in femur	NAD	
Total bilirubin (mg/dL)	19	16	4.4	5.5
ALP (IU/L)			2211	1099
GGT (IU/L)	163	105	555	316
Albumin (g/dL)	2.1	2.4	2.9	2.7
PELD score	22	31.4	32	22
Underwent LT?	Yes	Yes	Yes	No
Age at LT (mo)	50	33	28	–
Indication for LT	DCLD, PHTN	DCLD, PHTN	DCLD, PHTN	–
Latest PET-CT	–	NAD	–	Intermediate response in mediastinum; NAD elsewhere
Follow-up (mo)	20	38	3	12
Status	On follow-up	On follow-up	On follow-up	On follow-up

Abbreviations: AD, active disease; ALP, alkaline phosphatase; DCLD, decompensated chronic liver disease; GGT, gamma glutamyl transferase; LCH, Langerhans cell histiocytosis; LN, lymph node; LT, liver transplantation; NAD, no active disease; PELD, pediatric end stage liver disease; PET-CT, positron emission tomography and computed tomography; PHTN, portal hypertension.

transplantation at remission. Chemotherapy was resumed after transplantation to complete 52 weeks of treatment. Patient 4 had a complete resolution of active disease in the risk organs; however, he remained stable in mediastinal disease. He was positive for the BRAF-V600E mutation. Hence, trametinib was added at a dose of 0.025 mg/kg/d to the maintenance therapy.[15] His liver function stabilized after induction chemotherapy and hence he was continued with maintenance chemotherapy. His periodic monitoring schedule involved checking liver function every 3 months, cardiac function every 6 to 23 months, and assessing for other potential side effects, such as colitis, hemorrhagic events, skin rashes, and pulmonary signs and symptoms, during each visit. We plan to continue trametinib for 2 years (►**Table 1** and ►**Fig. 2**).

Discussion

In this cohort, low-dose cytarabine-based chemotherapy was administered to the children with LCH and progressive liver dysfunction. All four children successfully tolerated chemotherapy and attained remission. After achieving complete remission, three patients underwent liver transplantation. One child had stable disease in the mediastinum but had achieved complete resolution of the disease elsewhere. Following a multidisciplinary meeting, the treatment regimen was updated to include trametinib. This medication halts the MAPK pathway by inhibiting the activity of MEK1 and MEK2, thereby disrupting intracellular cell signaling that fosters tumor growth.[16] A correspondence published in the *British Journal of Haematology* in 2014 highlighted the remarkable outcome of low-dose cytarabine-based treatment, which is comparable to the results of the present study.[13] In a study conducted by Menon et al, low-dose cytarabine-based chemotherapy was employed in children with progressive liver dysfunction, demonstrating excellent results with this regimen.[5]

Conclusion

We propose that low-dose cytarabine/prednisolone-based regimen could serve as an appealing and less toxic alternative for children with active LCH and decompensated liver diseases. The low-dose cytarabine/prednisolone regimen is a well-tolerated chemotherapy regimen, with excellent outcomes. However, a large-scale prospective study is required to underpin this modified regimen and propagate its utility. If liver dysfunction persists, liver transplantation should be

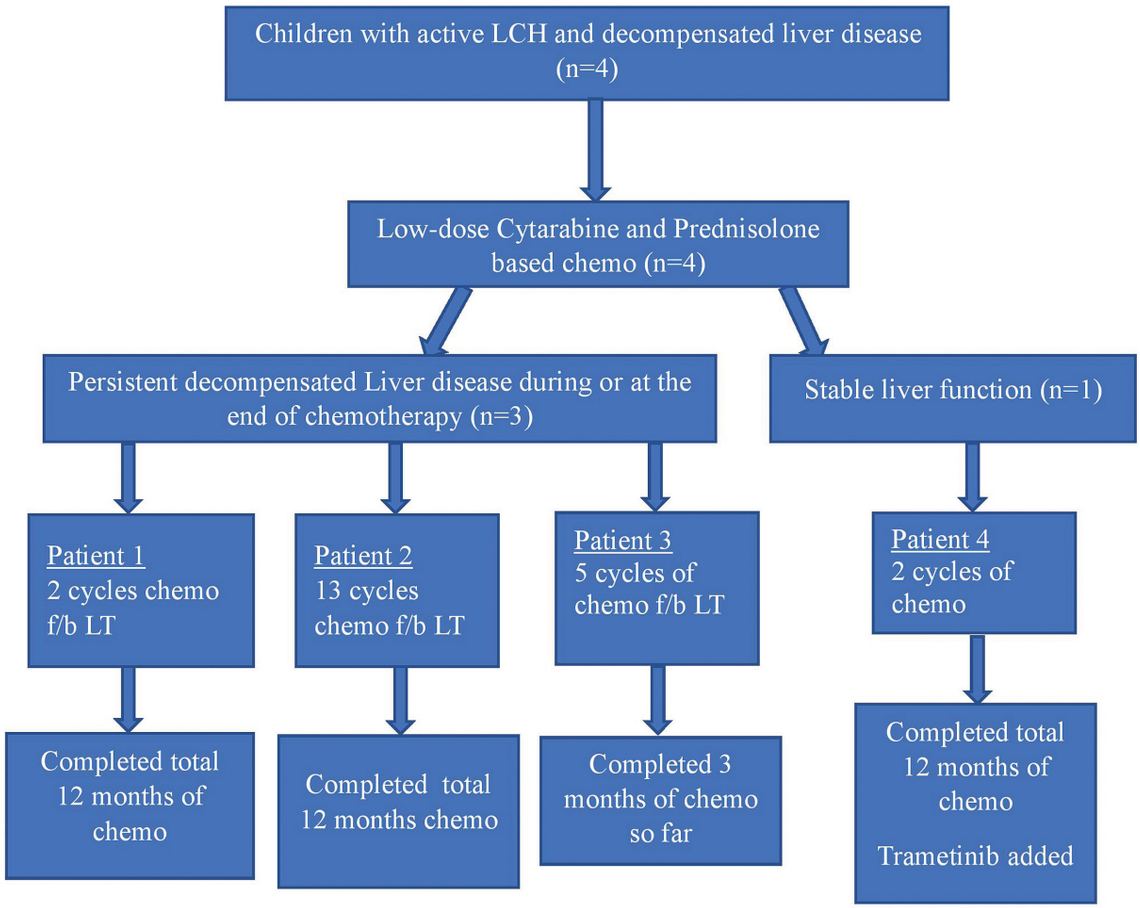

Fig. 2 Flowchart depicting the status of the liver disease and treatment received by the children. f/b = followed by; LT = liver transplantation; chemo = chemotherapy.

offered at complete remission to improve survival in these children.

Author Contributions

We state that all authors have contributed to the manuscript in significant ways, have reviewed and agreed upon the manuscript content.

N.G.H. contributed to the design of the study, literature studies, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, and manuscript editing. M.S.S. contributed to the concept and design of the study, definition of intellectual content, literature studies, manuscript preparation, manuscript editing, and manuscript reviewing. V.K.G. contributed to the concept of the study, definition of intellectual content, manuscript editing, and manuscript reviewing. D.M. contributed to the concept of the study, definition of intellectual content, manuscript editing, and manuscript reviewing.

Patient Consent

Patient consent was obtained.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgments

We acknowledge all the participants of the study. We extend our gratitude toward the faculty of the pediatric subspecialties—consultant pathologists, consultant radiologists, consultant biochemists, and many others. We are grateful for the contribution of the paramedical and nursing staff to patient management.

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A Rare Occurrence of Solid Gynecological Malignancy Synchronous with Hematological Malignancy: Rare Case and Review of Literature

Rubi Gupta[1] Pariseema Dave[1] Bijal Patel[1] Remi Abdul Shukur[1]

[1] Department of Gynaecological Oncology, Gujarat Cancer & Research Institute, Ahmedabad, Gujarat, India

Ind J Med Paediatr Oncol 2024;45:439–442.

Address for correspondence Pariseema Dave, Prefessor and Head of The Department of Gynaecological Oncology, Gujarat Cancer & Research Institute, Ahmedabad, Gujarat, India (e-mail: pariseema.dave@gcriindia.org).

Abstract

A synchronous solid and hematological malignancy is an uncommon condition in which a patient develops two or more primary cancers, one of which is a solid malignancy and the other one is a hematological malignancy, within 6 months of primary cancer diagnosis. The most common histology in solid malignancies is gastrointestinal adenocarcinoma, which coexists with the lymphoma subtype diffuse large B-cell lymphoma (DLBCL). Here, we report an extremely rare combination of serous carcinoma of the ovary synchronous with lymphoma of DLBCL subtype. A woman aged 52 years presented with an abdominal mass and abdominal pain for a short duration of 15 days. She was evaluated using clinical, radiological, and biochemical parameters. She was diagnosed with non-Hodgkin lymphoma by tru-cut biopsy from a bony lytic lesion and ovarian cancer by staging laparotomy. R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone) chemotherapy for lymphoma and staging laparotomy for persistent adnexal mass resulted in complete remission of both ovarian cancer and lymphoma. She received paclitaxel and carboplatin-based postoperative chemotherapy as an adjuvant for ovarian cancer.

Keywords

- synchronous multiple primary malignancies
- lymphoma
- serous ovarian cancer

Introduction

Synchronous tumors account for less than 5% of all malignancies. The prevalence of synchronous tumors in one patient ranges between 0.73 and 11.7%.[1] It is an extremely rare form of hematological malignancy. Synchronous tumors are defined as tumors that appear within 6 months of one another. They could be in the same or separate organs.[2] To define synchronous malignant tumors, consider the following: metastasis should not be present, both tumors must exhibit malignancy criteria, and they must differ pathologically from one another.[3] The coexistence of gynecological solid tumors with hematological malignancy is a very rare combination. We report a case of non-Hodgkin lymphoma diffuse large B-cell lymphoma (NHL DLBCL type) with serous carcinoma of the ovary. To the best of our knowledge, this is the first case of synchronous NHL (DLBCL) and ovarian serous carcinoma in the present literature. The most common and aggressive subtypes of NHL and carcinoma ovary are DLBCL and high-grade serous carcinoma, respectively. Three to four percent of DLBCL had synchronous multiple primary malignancies (MPMs).[4] We discuss management, prognosis, and the complicated hospital course that resulted in the diagnosis of synchronous primary malignancies.

Case Description

A woman aged 52 years with a history of ischemic heart disease was presented with abdominal pain and abdominal mass for the past 15 days. Per abdomen clinical examination,

article published online
October 3, 2023

DOI https://doi.org/10.1055/s-0043-1775830.
ISSN 0971-5851.

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

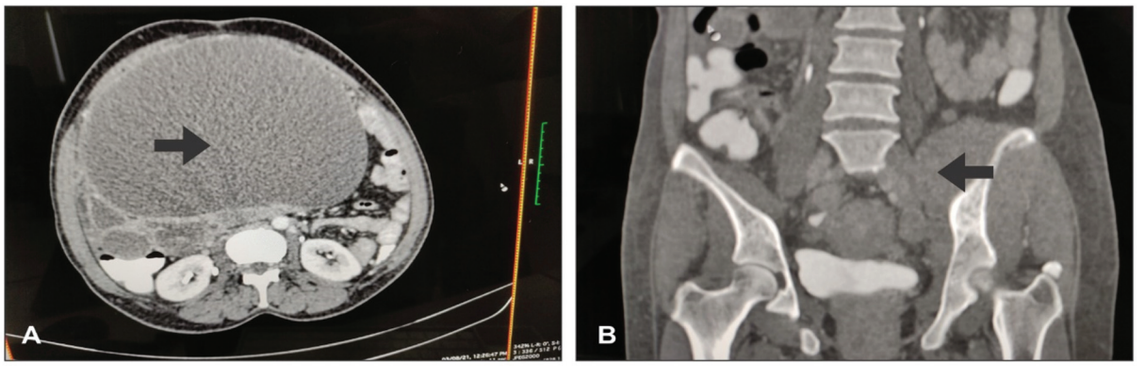

Fig. 1 (**A**) Cystic adnexal mass. (**B**) A bony lytic lesion with muscle infiltrates on computed tomography (CT) scan.

radiological imaging, and tumor markers were used to assess her for the same. Clinical findings suggested a smooth, mobile mass of 32 weeks in size. A computed tomography (CT) scan of the abdomen, pelvis, and thorax revealed a solid cystic mass 19×20 cm (right), 7×8 cm (left) (►**Fig. 1B**), ascites with omental, muscle, and pleural infiltrates, and a lytic metastatic lesion (50×25 mm) at the left iliac bone (►**Fig. 1A**). CA125 was 944 IU/mL, carcinoembryonic antigen was 17.3 ng/mL, and CA19-9 was 41.9 IU/mL. Due to extensive disease involving the muscle and pleura, the decision for neoadjuvant chemotherapy was made with a plan of ultrasound-guided biopsy from the lesion.

Although an ovarian tissue biopsy was negative for malignancy, ascitic fluid cytology and cell block were suspicious for malignancy. Again, a repeat omental biopsy revealed no evidence of malignancy with borderline epithelial tumor component. A third biopsy from a different suspicious area was recommended to confirm the diagnosis. This biopsy of a bony lytic lesion with muscle infiltrates showed a monotonous population of large-sized cells arranged in sheets with abundant apoptosis indicating NHL B-cell type, and immunohistochemistry (IHC) panel (positive for LCA, CD-20, BCL-6, and PAX-5 and negative for WT1, CD2, BCL-12, and MUM1) confirmed the diagnosis of diffuse large B-cell lymphoma, germinal center type (►**Fig. 2A and B**). A bone marrow biopsy revealed no evidence of malignancy and confirmed the primary lymphoma (NHL).

The case was discussed in the tumor board, and it was decided that at first chemotherapy for aggressive hematological malignancy would be administered, followed by an evaluation for ovarian mass presumed borderline epithelial malignancy. She underwent one cycle of cytoreduction CVP (cyclophosphamide, vincristine, prednisolone) followed by six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone)

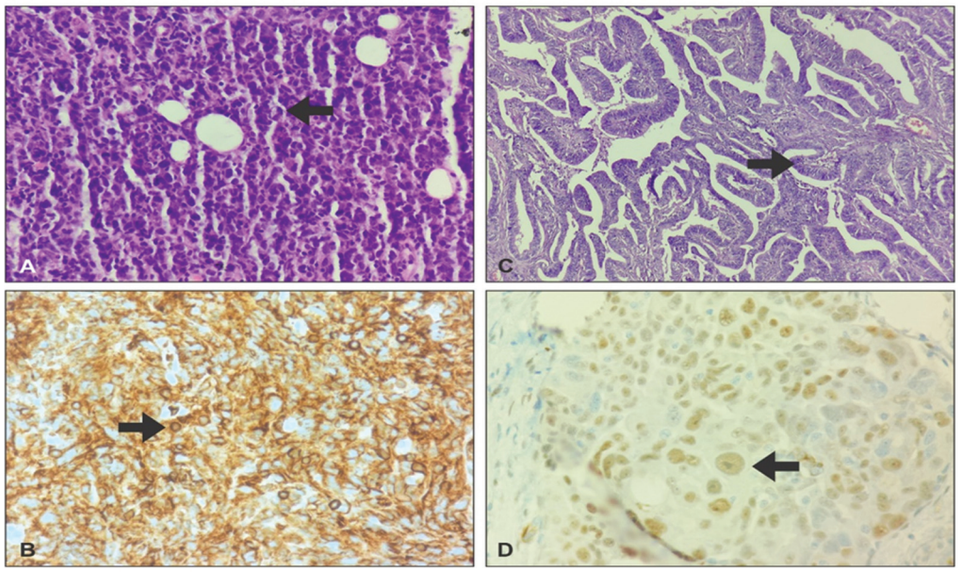

Fig. 2 (**A**) Hematoxylin and eosin (H&E) staining showing the sheet of atypical large lymphoid cells with hyperchromatic nuclei and eosinophilic cytoplasm with brisk apoptotic and mitotic activity for non-Hodgkin lymphoma (NHL). (**B**) Immunohistochemistry (IHC) showing membranous CD20 positivity. (**C**) High-grade (HG) nuclei with papillary architecture on final surgical specimen. (**D**) WT1 positive on IHC for final surgical specimen.

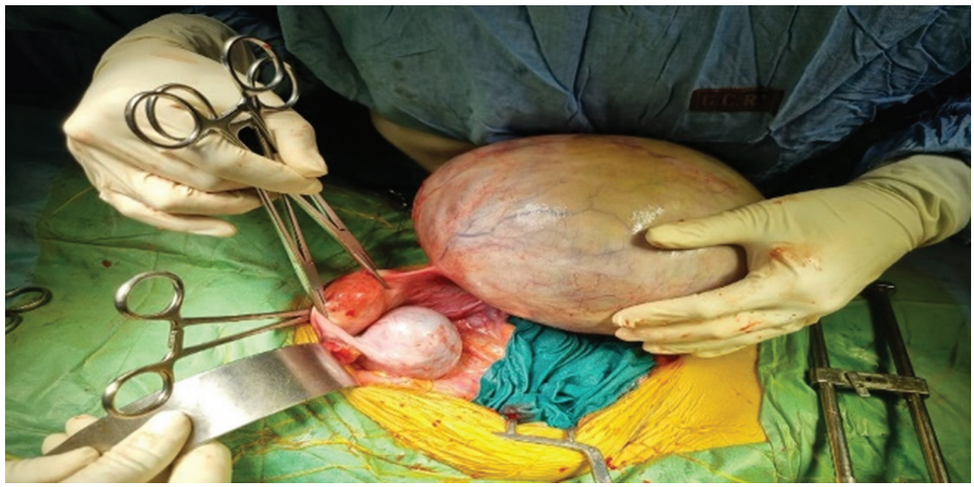

Fig. 3 Intraoperative finding.

regimen chemotherapy. Dose modification (10% dose reduction) was required after the fifth cycle of R-CHOP due to grade 3 thrombocytopenia. The size of the bony lesion reduced on CT evaluation, but the size of the adnexal mass remained unchanged. Positron emission tomography-CT imaging revealed a bilateral adnexal mass with a maximum uptake of 4.0 and no metastatic lesion elsewhere. As a result, she underwent interval cytoreductive surgery, including abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and deposit removal from the pouch of Douglas as much as possible. It was suboptimal surgery leaving residual tumor at the mesentery and pouch of Douglas. ►**Fig. 3** depicts an intraoperative finding (uterus with bilateral ovarian masses, one predominantly cystic, and another predominantly solid).

The final pathology specimen revealed high-grade serous ovarian carcinoma with a 3-cm omental carcinomatous deposit (FIGO stage IIIc). IHC panel confirmed high-grade serous carcinoma of the ovary (positive for WT1, AE1) and no lymphomatous metastasis to the ovary (negative for LCA) (►**Fig. 2C and D**).

She received and well-tolerated six cycles of adjuvant chemotherapy (paclitaxel and carboplatin) without dose modification. The patient received involved-field radiation therapy for residual bony lesions and backache. Complete remission of both lymphoma and ovarian cancer with treatment was achieved. She is on regular follow-up as per guidelines.

Discussion

MPMs are two or more cancers diagnosed at the same time or within 6 months of each other. A solid tumor is a mass of abnormal cells that develops in an organ or tissue, such as the breast, lung, or colon. Hematological cancers, such as leukemia, lymphoma, and myeloma, are cancers that affect the blood cells or the lymphatic system.[5] Solid malignancy with hematological malignancy can arise in various combinations and locations. The incidence of this synchronous type of malignancy is extremely rare, with only case reports or series available in literature. We also report a case of dual solid and hematological malignancy in one patient, at Gujarat Cancer and Research Institute in Ahmedabad with a very common presentation of a pelvic mass. To the best of our knowledge, this is the first reported case of synchronous NHL (DLBCL) and serous carcinoma of ovary in one patient. The most common location of primary solid malignancy associated with NHL is the gastrointestinal tract (esophagus to rectum), followed by the prostate, lung, and breast.[6] The synchronous association of solid tumors of ovary with hematological malignancy is one of the rarest forms of MPMs. In our case, diagnosis of DLBCL was made initially, while there was suspicion of second malignancy due positive ascitic fluid cytology for malignancy and borderline surface epithelium malignancy on tru-cut biopsy from adnexal mass. Diagnosis of serous carcinoma of the ovary was confirmed after cytoreductive surgery and final histopathology of surgical specimen. Finally, ovarian serous carcinoma was treated sequentially within 6 months of primary diagnosis of DLBCL.

The pathogenesis of synchronous MPM is not well understood. There are several theories, such as different types of tumors arising from the same precancerous lesion, genetic instability, or a defect in the mismatch repair system.[7] It has been proposed that lymphomas may cause lymphatic channels to be obliterated, allowing synchronous solid neoplasms to grow.

A rare occurrence of synchronous malignancy can bring distinct diagnostic and treatment issues. Diagnosis of synchronous MPMs can be difficult and challenging. It is unrealistic to get a biopsy for every metastatic lesion, but re-biopsy should be considered for any atypical and uncommon metastatic lesion with keeping in mind the biological behavior of primary malignancy. As in our case, bone and muscle infiltrates were not typical finding for carcinoma ovary. Therefore, the decision to do a repeat biopsy from these muscle infiltrates with lytic

bony lesion was made to look for another malignancy, which subsequently revealed DLBCL.

It is very challenging to choose the best treatment plan when a patient has two different types of cancer. Each type of cancer may need different modalities of treatment. Additionally, treatment of one type of cancer may make the other type worse, so selecting a treatment strategy requires considerable thought. For synchronous lymphoma and ovarian cancer, there is no established treatment plan. Utilizing tumor board discussions, treatment was prioritized and tailored to the patient based on the tumor's aggressiveness and likelihood of responding to primary therapy, ensuring a multidisciplinary team approach. A high level of aggressiveness was present in both the primary (DLBCL and serous carcinoma), which added to the poor prognosis. Because of its aggressive behavior and confirmed diagnosis, lymphoma DLBCL type was treated first with chemotherapy regimen R-CHOP. This regimen includes cyclophosphamide and Adriamycin (doxorubicin) which is also part of CAP (cyclophosphamide, Adriamycin, and platinum) regimen, previously utilized in advanced untreated ovarian cancer.[8] This cyclophosphamide-containing regimen was also beneficial for response in ovarian cancer when treating hematological malignancy first, which worked as a neoadjuvant for solid ovarian malignancy.

Our success in treating this dual malignancy is proof that multidisciplinary teams can work together effectively to produce positive result. Due to the complexity of this condition and the scarcity of reported cases, research and clinical studies are essential to further understand its underlying mechanisms, optimal diagnostic approaches, and treatment options.

Conclusion

Synchronous solid and hematological malignancy is a rare entity. We should have a high index of suspicion when dealing with such complex situations. We should also consider performing another biopsy if clinical and radiological findings are not typical for primary malignancy. Appropriate selection of chemotherapy regimen that could be useful in both malignancies is necessary as in our case selection of regimen containing cyclophosphamide and Adriamycin. Multidisciplinary coordination and expertise are problem-solving tools.

Patient Consent

During file release, general consent of the file includes that the biological content of the patient could be part of the research. Nondisclosure of a patient's identity, either in the form of name or photograph.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgments

We would like to express our deepest gratitude to the medical oncologists who have contributed to managing this case.

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Pregnancy and Acute Lymphoblastic Leukemia: A Case Series and Review of Literature

Sukrita Bhattacharjee[1] Shouriyo Ghosh[2] Siddhartha Sankar Ray[1] Sambit Samanta[1] Nilanjan Sinha[1] Sandeep Saha[3] Maitreyee Bhattacharyya[1]

[1] Institute of Haematology and Transfusion Medicine, Medical College Kolkata, West Bengal, India
[2] L/BMT Program, Vancouver General Hospital, Vancouver, Canada
[3] Department of Clinical Haematology, NRS Medical College, Kolkata, West Bengal, India

Address for correspondence Maitreyee Bhattacharyya, MBBS, MD, DM, Institute of Hematology and Transfusion Medicine, Medical College Hospital, 88, College Street, Kolkata 700073, West Bengal, India (e-mail: mbhattyacharyya@yahoo.co.in).

Ind J Med Paediatr Oncol 2024;45:443–450.

Abstract

Acute lymphoblastic leukemia (ALL) diagnosed during pregnancy is rare and causes ethical and therapeutic challenges. We performed a retrospective search of ALL patients ($n = 202$) treated at our institution from 2015 to 2020 and found five patients diagnosed during pregnancy. In this report, we discuss the individual patients in detail and the challenges faced during their treatment. The use of established lymphoblastic leukemia treatment protocols and the modifications made therein to prevent untoward chemotherapy-related toxicities to the fetus are discussed in this study. We report the second use of rasburicase during pregnancy in literature with favorable maternal and fetal outcomes. We also present an extensive literature review of 41 cases of ALL in pregnancy previously reported. It is important to note that there is a dearth of guidelines for the treatment of these complex situations, and although certain general principles can be established, an individualized approach is needed in most cases of leukemia diagnosed during pregnancy.

Keywords
- acute leukemia
- ethical considerations
- pregnancy
- maternal well-being
- fetal outcome
- chemotherapy

Introduction

Acute leukemia is uncommonly encountered during pregnancy, occurring in approximately 1 in 75,000 cases and its management is a challenging task.[1] It requires a multidisciplinary approach to treat this life-threatening condition, keeping in mind the health and well-being of the mother and fetus. Patient management entails a gamut of challenges from treatment decisions to ethical and social considerations. Moreover, there is a dearth of trials in this unique and rare cohort of patients. Data from case reports, case series, and retrospective studies are the only evidence available, thereby emphasizing the need for an individualized approach.

Herein we report five cases of acute lymphoblastic leukemia (ALL) diagnosed during pregnancy at our center and challenges faced in managing these patients. We also reviewed the available literature to summarize the data on the clinical presentation, treatment complications, maternal, and fetal outcomes of these patients.

This is a series of ALL patients presenting during pregnancy who were treated at our institute between January 2015 and July 2020 (5 years). Clinical and laboratory data and outcomes of these patients were retrieved from our archives and reviewed for the purpose of this report. Informed consent was taken from the patients and/or next of kin while reporting these cases. For each patient, an institutional medical board, comprising specialists from hematology, obstetrics, neonatology, anesthesiology, and transfusion medicine, was convened to formulate the management plan. For the management of ALL in the adolescent and young

article published online
May 17, 2023

DOI https://doi.org/10.1055/s-0043-1766129.
ISSN 0971-5851.

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

adults age group, our institutional practice is to use pediatric inspired protocols, namely, the Berlin Frankfurt Munster-2002 regimen. Our institute has a state-of-the art neonatal intensive care unit that can manage preterm births as early as 25 weeks of gestational age.

A total of 202 ALL patients were treated during the period 2015 to 2020 at our institution of which five were ALL with pregnancy (B-ALL, $n = 4$; Philadelphia positive B-ALL, $n = 1$). All five cases were women aged between 20 and 29 years (median age: 26 years) of whom three were primigravidae. None of the patients were diagnosed in the first trimester ($n = 2$, third trimester, $n = 3$, second trimester). The first two patients involving late third trimester mothers with newly diagnosed ALL were relatively stable and therefore could be managed with transfusion support till delivery, after which standard chemotherapy was administered. In the other three patients, chemotherapy had to be started with the fetus in-utero as a life saving measure for the mother. Institutional protocol for ALL induction therapy comprised of prednisolone at 60 mg/m^2, vincristine at 1.4 mg/m^2, daunorubicin at 30mg/m^2, and L-asparaginase at 5000 IU/m^2 in accordance with the BFM-2002 protocol in phase IA and 6-mercaptopurine, cyclophosphamide, and cytarabine in phase IB, followed by consolidation, re-induction and maintenance treatment limbs.

Case Series

Patient 1: A 28-year-old third gravida (32 weeks gestation) who presented with anemia was diagnosed with intermediate-risk Philadelphia negative pre-B-ALL. Her pregnancy was supported till 37 weeks with transfusions after which she delivered a healthy male baby by normal vaginal delivery (NVD). Subsequently BFM-2002 protocol was started and the induction was complicated by recurrent episodes of maxillary sinusitis, sepsis (Klebsiella species), and central line associated blood stream infection, which were managed with appropriate antibiotics. Subsequent phases of chemotherapy were administered without any interruptions.

Patient 2: A 24-year-old primigravida at 35 weeks gestation, developed intermittent fever, and generalized weakness of 1 month duration and was diagnosed as intermediate risk pre-B-ALL. Similar to patient 1, she was also kept on supportive care with packed red blood cells and platelets till she delivered a healthy male child by NVD at 37 weeks gestation. Subsequently, she was initiated on BFM-2002 protocol and received chemotherapy without any modifications.

Patient 3: A 29-year-old primigravida at 28 weeks of gestation was diagnosed as Philadelphia negative pre-B-ALL with leucocytosis (50,000/cumm with 80% blasts) and retinal hemorrhage. She received BFM-2002 induction without any modifications. Fetal assessment during leukemia induction revealed no anomalies. At 35 weeks of gestation and at the end of induction IA when her counts had recovered, she underwent planned Cesarean Section (CS) and delivered a healthy baby boy, appropriate for gestational age. Subsequently she received phase IB of BFM-2002. She unfortunately relapsed post-induction, and therapy was switched to rituximab-hyper-CVAD (comprising of hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone). During the second cycle of hyper-CVAD, she developed febrile neutropenia, septic shock, and succumbed to it. The child was healthy at last known follow-up.

Patient 4: A 26-year-old third gravida (26 weeks) presented with fever, generalized lymphadenopathy, and multiple skin nodules and plaques. On evaluation, she had hyperleukocytosis (with 90% blasts), anemia, and thrombocytopenia and was diagnosed as Philadelphia positive (Ph +) B-ALL with leukemia cutis and central nervous system (CNS) involvement. She developed tumor lysis syndrome (TLS) and was given rasburicase during initial stabilization. She was then started on modified E-WALL protocol which included a tyrosine kinase inhibitor (TKI)—imatinib 600 mg daily along with weekly pulsed dexamethasone and vincristine injections. Intrathecal chemotherapy was given with cytarabine and hydrocortisone, while methotrexate was omitted. Her platelet counts recovered by 31st week of gestation. Her pregnancy was continued till 32 weeks of gestation after which she underwent an elective CS and gave birth to a healthy female child. Post-induction bone marrow on day 52 of E-WALL protocol was in morphological remission and BCR-ABL measurable residual disease (MRD) was negative. She received one cycle of E-WALL consolidation after which she was lost to follow-up.

Patient 5: The last case is that of a 20-year-old primigravida at 24 weeks gestation who presented with progressive weakness, exertional dyspnea, low-grade fever, and was found to have severe anemia and atypical cells in peripheral blood. A diagnosis of Ph negative pre-B-ALL was made. She developed hepatic encephalopathy, TLS, and septic shock that were managed effectively. In this background of deranged liver functions and an early pregnancy, she was started on a modified BFM-2002 protocol, consisting of steroids and vincristine only. Subsequently, she went on to receive a modified phase IB of BFM-2002 protocol where only the cytarabine blocks were administered intravenously and intrathecal cytarabine chemotherapy was given, while omitting methotrexate, 6-mercaptopurine, and cyclophosphamide from the protocol. Her phase IB of induction was completed at 32 weeks of gestation. Pregnancy continued till term and she delivered a healthy male child. Post-induction, bone marrow was in remission and MRD was negative. However, she had persistence of CNS disease and was given high-dose intravenous methotrexate consolidation @ 5gm/m^2 along with triple intrathecal chemotherapy. Her reinduction chemotherapy phase was interrupted by coronavirus disease 2019 pandemic. Subsequently on resumption of chemotherapy, she developed febrile neutropenia, macrophage activation syndrome, went into septic shock, and unfortunately succumbed to her illness.

A summary of the patients, course of treatment in hospital, and their outcome are mentioned in ►**Table 1**.

Table 1 Patient characteristics, disease and pregnancy details, protocol and modifications used, issues faced, and fetomaternal outcomes

Case no.	Patient details (age/obstetric history/POG)	Presenting counts (Hb [g/dl]/total leucocyte count (cumm)/platelets (cumm)/blast [%])	Diagnosis IPT/CNS status/ Ph status/CG/ risk group/ EM disease	Protocol	Indication for treatment; modification done	Significant Issues faced during treatment	Disease outcome	Pregnancy outcome	Last follow-up
1	28 y G3P2 32 weeks	9.1/41,500/20,000/ 50% blasts	Pre-B-ALL/CNS-1/ Ph- neg/46XX/IRG	BFM-2002	Protocol started post-delivery No dose adjustments	Induction: Maxillary sinusitis, CLABSI and sepsis	Remission	NVD, male baby@37 weeks gestation	4 years: mother and child doing well
2	24 y G1P0 35 weeks	9.4/10600/218,000/ 30% blasts	Pre-B-ALL/ CNS-1/ Ph- neg/ 46XX/ IRG	BFM-2002	Protocol started post-delivery Vinblastine given in view of peripheral neuropathy	Induction- CLABSI, genital herpes, pneumonia, vincristine induced PN	Remission	NVD, male baby@ 37 weeks gestation	3 years: mother and child doing well
3	29 y G1P0 28 weeks, 4 days	8.3/50000/20000/ 80% blasts	Pre B-ALL/CNS-1/ Ph- neg/NDC/IRG	BFM-2002	Protocol started in third trimester in view of bleeding. No dose modification. Phase IB given post-delivery	Induction- cytopenia Relapsed prior to consolidation. Switched to Hyper-CVAD.	Relapse post-induction 2# Hyper-CVAD: death due to septic shock	Elective CS Male baby @ 35 weeks	Child was healthy at last follow-up
4	26y G3P2 26 weeks	7/250,000/10,000/ 90% blasts	Philadelphia +ve B-ALL/CNS-3/ 46XX/HRG/ leukemia cutis	Modified E-WALL; Imatinib 600 mg OD	Induction started in late second trimester. Rasburicase given IT: ARA-C and hydrocortisone. MTX omitted	TLS	Remission	Elective CS, female baby@ 32 weeks	Lost to follow-up after first cycle of consolidation
5	20y G1P0 24 weeks	6/84,600/25,000/ 40% blasts	Pre-B-ALL/CNS-1/ BCR- ABL neg/ 46XX/IRG	BFM 2002 with changes	Induction: second trimester: VCR and steroid only IB: Only Ara-C; IT ARA-C Consolidation: MRC UK-ALL HD-MTX @ 5gm/m^2 and L-ASP 10000 IU/m^2 triple IT with MTX, ARA-C and hydrocortisone	Pre-treatment: Hepatic encephalopathy, septic shock, TLS Consolidation: CNS relapse Reinduction: therapy interruption due to COVID-19 pandemic	Remission post-induction Consolidation: Isolated CNS relapse Re-induction: Death due to septic shock and MAS	Elective CS, male baby@ 37 weeks	Child healthy at the time of her death

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin Frankfurt Munster; CLABSI, central line associated bloodstream infection; COVID-19, coronavirus disease 2019; CNS, central nervous system; CS, cesarean section; EM, extramedullary; IPT, immunophenotype, IRG, HRG, intermediate and high-risk groups respectively; MAS, Macrophage Activation Syndrome; NDC, nondividing cells in cytogenetics; NVD, normal vaginal delivery; POG, Period Of Gestation; RDP, random donor platelets; PN, peripheral neuropathy; TLS, tumor lysis syndrome; IT, Intrathecal Chemotherapy.

Discussion

Among leukemia cases encountered in pregnancy, around 28% cases of leukemia in pregnancy are ALL, the rest being acute myeloid leukemia (AML) and chronic myeloid leukemia, (CML).[1] The major concern in the management of these cases has been the optimal timing and dosing of chemotherapy so as to prevent harmful effects to the fetus. An extensive search of the literature revealed 41 cases of ALL in pregnancy (summarized in ►**Table 2**)[2–12] in addition to the 60 cases of ALL during pregnancy described by Cardonick and Iacobucci.[3] Pregnancy leads to physiological changes such as increased plasma volume as well as changes in drug pharmacokinetics due to altered hepatic and renal clearance of drugs. Pregnancy can also change drug metabolism by creation of a third space in the form of the amniotic sac.[13]

Table 2 Synopsis of cases of pregnancy with acute lymphoblastic leukemia reported in literature

Sl. no.	Reference (total cases; ALL cases)	Patient details (age/obstetric history/POG)	Diagnosis	Therapy used; modifications (if any)	Pregnancy and fetal outcome	Disease status	Maternal outcome
1	Krueger et al [1976] (4)	15/-/26	ALL	COAP regimen: cyclophosphamide, vincristine, cytarabine, prednisone	Induction of labor. Normal Infant at 38 weeks	PD	Relapse1-month post-partum
2	O' Donnell et al [1979] (4)	24/-/15	ALL	TAD regimen (thioguanine, cytarabine, daunorubicin)	Pre-eclampsia and intrauterine fetal death at 30 weeks	CR	Alive
3	Okun et al [1979] (5)	18/-/12	ALL	1st Induction: VCR, Pred, IT MTX. 2nd induction: CTX, L-Asp, DNR, 6-mercaptopurine; WBRT	CS at 31 weeks; baby with transient pancytopenia, CHF, normal development at 1 year	Relapse	CNS relapse 5 weeks post-partum
4	Dara et al [1981] (4)	26/-/21	ALL	6-MP, MTX, discontinued when pregnancy confirmed; relapse at 21 weeks, second line initiated with doxorubicin, VCR, Pred, Cyt, MTX	CS at 36 weeks. infant with polycythemia and hyperbilirubinemia Normal growth and development at 6 months	CR	Alive
5	Sigler et al [1988] (4)	26/-/32	ALL	Pre, DNR, Ctx, Cyt, L-asp	Induction at 35 weeks. Normal infant	CR	Remission followed by maintenance
6	Avasthi et al [1993] (4)	20/-/22	ALL	Two courses of VCR, Pred	Preterm delivery at 29 weeks to live infant	–	Sudden death 2 days after delivery
7	Camera et al [1996] (4)	21/-/17	ALL	VCR, Pred, DNR, L-asp	C-section at 29 weeks Normal male infant	Relapse	Death 9 months later from relapse
8	Tewari et al [1999] (4)	17/-/33	ALL	VCR, Pred for relapse ALL	Induction at 35 weeks Normal infant	CR	Consolidation s/p allo-SCT 22 months later
9	Hansen et al [2001] (4)	24/-/26	ALL	Induction CALGB 9111. At 26 weeks: DNR, VCR, Pred, L-asp At 30 & 34 weeks: IT-MTX, Ctx,6-MP, Cyt, VCR, L-asp	Spontaneous delivery at 36 weeks. Normal male infant	–	Unclear
10	Ali et al [2002] (10 cases: 2-ALL) (5)	24/G1/24 21/G2P0/8	B-ALL Relapsed B-ALL	Not documented Not documented	Therapeutic abortion Therapeutic abortion	Remission relapse	Alive Dead
11	Terek et al (2003] (4)	21/-/31	ALL	VCR, DNR, Pred, L-asp	C-section, newborn respiratory distress (required intubation)	–	Maternal death due to sepsis
12	Chelghoum et al [2005] ($n = 37$) (6) 6 ALL cases	1. 25/G1/27 2. 34/G2/9 3. 33/G4/26 4. 30/G1/10 5. 21/G1/28 6. 25/G1/9	T-ALL Pre B-ALL Pre B-ALL Ph+ B-ALL Pre B-ALL T-ALL	All cases received VCR + Dauno + CTX + Pred	NVD, premature Therapeutic abortion CS; premature Therapeutic abortion CS; premature Therapeutic abortion	PD CR CR CR CR CR	
13	Molkenboer et al [2005] 2 ALL cases (7)	1. 30/G3P2/6 2. 37/G1/15	Ph+ B-ALL Ph+ B-ALL	Pred + VCR + Dauno + Asp + ITMTx; High-dose cytarabine+ imatinib Same as above	Missed abortion at 11 weeks Spontaneous delivery at 22 weeks; stillborn	CR PD post-induction	Death post-HSCT Imatinib palliation. Death few weeks later
14	Dilek et al [2006] (1/21, ALL) (8)	25/G1/term	ALL	4 drug regimen induction	NVD; LBW	CR post-induction	Alive

Table 2 (*Continued*)

Sl. no.	Reference (total cases; ALL cases)	Patient details (age/obstetric history/POG)	Diagnosis	Therapy used; modifications (if any)	Pregnancy and fetal outcome	Disease status	Maternal outcome
15	Matsouka et al [2007] (9)	16/G1/26 + 3d	B-ALL	BFM-95; Recombinant G-CSF use during cytopenic phase. Delivered post-induction	Elective CS at 32.4 weeks; LBW	CR	Alive
16	Papantoniou et al [2008] (4)	16/-/26	ALL	DNR, VCR, L-asp, Pred, IT-Mtx, G-CSF	CS at 32 weeks. Infant normal at 18 months	CR	Remission at 18-months follow-up
17	Udink Ten Cate et al [2009] (4)	30/-/23	ALL	VCR, Pre, IT-MTX, Ctx, DNR. VCR, Ctx, DNR. Maintenance 6-MP	PROM at 33 weeks, NVD baby; pancytopenic, normal development at 2 years	CR	MUD—HSCT In CR 2 years after transplant
18	Aljurf et al [2009] 2 ALL cases (4)	37/-/29 27/-/13	ALL ALL	VCR, dexamethasone, idarubicin Unknown	Full-term infant; anemia Spontaneous abortion at 14 weeks during induction	CR CR	CR with induction Allo-SCT in CR 1 Alive 4 years later
19	Ticku et al [2013] (4)	22/G1/26	Ph+ B-ALL	Induction: Hyper-CVAD + dasatinib Ph+ mutation F317L; Ponatinib started 10 days post-partum	Elective CS at 30 weeks; LBW	CR	Alive
20	Nakajima et al [2013] (10) 3 ALL cases	1. 20/G1/37 2. 36/G1/29 3. 29/G1/5	ALL ALL/ t(9;22) ALL	Not available DNR + VCR +, CTX + Pred Not available	Emergency CS; live birth Elective CS; live birth Therapeutic abortion	PD CR CR	Dead Alive Alive
21	Saleh et al [2014] ($n = 32$; 6 ALL cases) (2)	1. 23/G2/38 2. 25/G1/12 3. 26/G3/28 4. 23/G3/13 5. 37/G7/29 6. 21/G1/31	Pre B-ALL Pre B ALL Pre B-ALL Pre B-ALL Pre B- ALL T-ALL	None None 5 drug regime None 5 drug regime VCR + Pred	Live birth at term Spontaneous abortion Spontaneous abortion Spontaneous abortion Live birth at term Preterm birth at 33+ weeks	PD PD CR PD LTFU PD	Death Death Alive, post-SCT Dead, post-SCT LTFU Death
22	Farhadfar et al [2016] ($n = 23$) 5 ALL cases (11)	1. 26/-/12 2. 23/-/6 3. 34/-/10 4. 19/-/16 5. 28/-/35	B-ALL B-ALL Ph+ ALL B-ALL B-ALL	Post-termination induction C10403 Post-termination induction C10403 CALGB9111; Reinduction: Imatinib with ara-C HSCT: MUD, TBI/VP-16 DNR/VCR/Pred; Consolidation: HiDAC Post-delivery - DNR/VCR/Pred Relapse: DNR/VCR/Pred, HiDAC, MTX/L-Asp	Therapeutic abortion Therapeutic abortion Fetal loss at 19 weeks Fetal loss 22 weeks NVD,38 weeks	- CR CR, f/b HSCT CR PD	Alive Alive Death on D21 of HSCT d/t septic shock Death Death
23	Vlijm-Kievit et al [2017] (12)	37/G2P1/36	T-ALL	Pred + VCR + Dauno + Peg-asparaginase (HOVON 100 protocol)-Asp and MTX delayed till post-delivery Therapeutic LMWH given upto 6 weeks post-partum	NVD 37 weeks	Remission	Alive

Abbreviations: ALL, ALL, acute lymphoblastic leukemia; CR, complete remission; CS, cesarean section; CTX, cyclophosphamide; Cyt, cytarabine; DNR, daunorubicin; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; HSCT, hematopoietic stem cell transplant; IT, intrathecal; L-asp, L-asparaginase; LBW, low birth weight; LMWH, low molecular weight heparin; LTFU, lost to follow-up; MTX, methotrexate; MUD, matched-unrelated donor; NVD, normal vaginal delivery; PD, progressive disease; Pred, prednisone; VP-16–Etoposide; WBRT, whole brain radiation therapy.

Estrogen receptors like HL-60 have been found in human myeloblastic leukemia cell lines[14] however, pregnancy alone is not thought to have an adverse effect on leukemia.[13]

Management of leukemia in first trimester: In our study, none of the patients presented with leukemia in the first trimester. As per recommendations, the pregnancy should be terminated prior to initiation of chemotherapy (many recommend 20 weeks and earlier).[3,15] Another approach in precious pregnancies is to give a short course of steroids to carry forward the pregnancy past the period of embryogenesis, after which cytotoxic chemotherapy can be administered.[15] The limited evidence suggests that almost all chemotherapeutic drugs used in ALL induction can be given during pregnancy, albeit, with risks to the fetus including still-births, intrauterine growth restrictions, spontaneous abortions, and congenital malformations, especially in the first trimester.[15–17] Beyond first trimester, however, almost all chemotherapeutic drugs can be used. Some modifications

have also been recommended with regard to L-asparaginase and intrathecal methotrexate in view of risk of thromboembolism and fetal aminopterin syndrome.[18] In our literature search, we found 11 pregnancies in the first trimester with ALL, 8 of whom underwent therapeutic abortion prior to starting chemotherapy and 2 had spontaneous abortion and only 1 pregnancy resulted in a live birth (premature) where induction was with only vincristine and prednisolone.[4–6,10,12]

Management of leukemia in second trimester: In our report, both patients with second-trimester pregnancies presented with complications for which several key modifications were made and the results were favorable. In the fourth patient, presence of a targetable lesion (BCR-ABL) prompted us to use a TKI along with steroids and vincristine as per the E-WALL protocol.[19,20] Data from CML patients with pregnancy proves that TKIs are teratogenic when used during organogenesis and may also lead to adverse pregnancy outcomes when used in later trimesters. However, other studies have advocated the use of Imatinib safely in second and third trimesters of pregnancy.[21–23] Data on other second-generation TKIs are scanty with isolated cases of fetal exposure to dasatinib and nilotinib.[24,25] We, therefore, used imatinib, instead of dasatinib (as per the E-WALL protocol) for our patient.[19] There are six cases of Ph+ ALL described in ►**Table 2**, mostly treated with imatinib as the TKI of choice.[4,6,7,10] In one case, both dasatinib and ponatinib were used due to tyrosine kinase domain mutation. However, as chemotherapy was started post-partum, the effects of these drugs on fetal outcome cannot be commented upon.

The fifth patient in our cohort was also a second-trimester pregnancy, but she had multiple complications at diagnosis itself, precluding the use of full-fledged BFM-2002 protocol.[26] L-asparaginase was added to the consolidation limb of chemotherapy, similar to the UKALL and E-WALL consolidation protocols for the treatment of Ph+ ALL.[19,27] Of note, there is in vivo antagonism of methotrexate and L-asparaginase due to opposing mechanisms of action. This can be overcome by administration of L-asparaginase *after* (but, *not before*) high dose methotrexate. This prompted us to use it 24 hours after completion of methotrexate infusion.[28,29] Although the patient succumbed to infectious complications later-on during the course of treatment, both maternal and fetal outcomes of pregnancy were favorable.

Management of leukemia in third trimester: Chemotherapy should ideally be withheld 3 weeks prior to childbirth to allow the counts to recover at the time of delivery and also to prevent neonatal myelosuppression.[30] A planned delivery is always essential in these scenarios. Another option for patients presenting near term is to initiate preinduction with steroids alone and then continue with the full chemotherapy once the child is delivered.[31] A conservative approach with transfusion support till delivery was safely adopted for first two relatively stable patients presenting in late third trimester, while in the third patient, we started chemotherapy ante-partum. In the cited literature, we found two cases of third-trimester pregnancies diagnosed near term, in whom chemotherapy was started post-partum (►**Table 2**).

Supportive care: TLS is a common complication in highly proliferative hematological malignancies and is an oncologic emergency. Rasburicase use has not been deemed safe in pregnancy, in view of teratogenicity reports in animal studies. However, it has been used in cases where the benefits outweigh the risk.[32] The Ph+ ALL patient in our cohort presented to us with life-threatening TLS and after due consideration, we gave her rasburicase during induction and did not see any adverse fetal outcomes. To the best of our knowledge, only one earlier case of antepartum use of rasburicase has been published in literature at 35+ weeks of gestation in a case of ALL.[33]

Chemotherapy-induced neutropenia increases the chance of infections in the mother and poses numerous risks during pregnancy, both to the mother and the fetus. This is compounded by the fact that not all antibiotics can be used safely during this period.[13] Recombinant granulocyte colony-stimulating factor has been reported to be safe and can be used to shorten the period of neutropenia.[9,34] Leukemic patients may also present with thrombocytopenia that can be deleterious at the time of delivery, especially when the required platelet thresholds for vaginal (30,000/cumm) and cesarean delivery (50,000/cumm) are not met.[35,36]

In all our patients, fetal outcomes were favorable in terms of four babies being born at term either by NVD or elective CS. Only one baby was born prematurely at 32 weeks but is currently doing well. There is an association of intrauterine growth restriction and low birth weight (LBW) babies with exposure to chemotherapeutic agents in the second and third trimester. Preterm deliveries are also common. Prolonged durations of myelosuppression with their inherent complications such as infections have been observed in neonates born to mothers undergoing chemotherapy.[13] Long-term effects on growth and development of these children are also of concern and require follow-up of this rare and unique cohort. Among the 41 cases we reviewed in literature, there were 15 abortions (4 spontaneous, 11 therapeutic), 11 preterm/LBW babies, 1 still born, and 14 normal live births. In 23 cases, the fetuses were exposed to chemotherapy in utero and this resulted in four spontaneous abortions, sixteen LBW/preterm deliveries and fetal deaths. Some of these babies had complications at birth (►**Table 2**). Only three live healthy newborns were reported post-chemotherapy exposure in utero.

Post-delivery, due consideration should be given to breast feeding, future fertility, and reproductive health of the patient.[13] In most situations, breastfeeding is not recommended while the mother is on chemotherapy, as these agents can be secreted in breast milk. If at all breastfeeding is essential, it is recommended to commence at least 2 weeks after the last administration of chemotherapy.[15] Complications such as mastalgia and breast abscesses may arise and it is therefore recommended for lactating mothers on chemotherapy to express and discard the milk to prevent such issues. Fertility issues in surviving patients may also arise, and similar to any woman in the reproductive age-group undergoing chemotherapy, it is recommended to give a hiatus of at-least 2 to 3 years after completion of chemotherapy to try to conceive once again.[16]

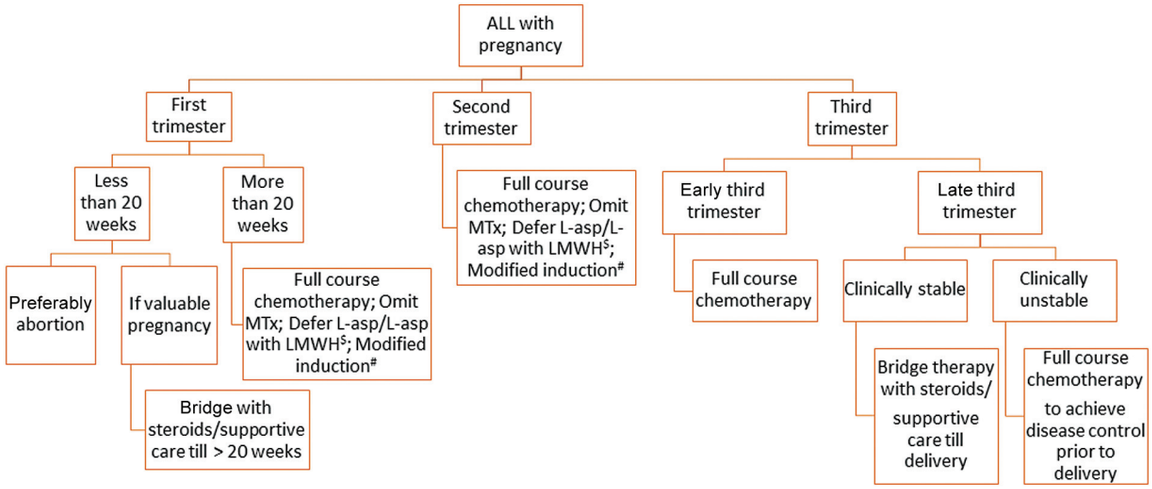

Fig. 1 Flowchart of management of acute lymphoblastic leukemia in pregnancy. $: L-asparaginase is associated with increased risk of thrombosis during pregnancy and should be combined with low molecular weight heparin (LMWH) prophylaxis or deferred till after delivery. #: Modification of protocol on a case-to-case basis; modification based on co-morbidities/intolerance to specific chemotherapeutics.

Saleh et al in their follow-up of 32 patients opined that acute leukemia patients had poorer long-term outcome compared to nonpregnant patients. Given the small number of patients in our cohort, we are unable to comment on this aspect.[2] Our experience shows that those patients who received full dose chemotherapy post-delivery were able to maintain remission and probably reflect the requirement of more aggressive therapy post-delivery to prevent relapse.

The cases described here were unique with respect to several factors including the time of presentation, clinical and leukemia risk profile, and complications. Hence, an individualized approach was undertaken. A proposed algorithm for the management of ALL in pregnancy is described in ►**Fig. 1**.

Conclusion

Management of leukemia in pregnancy is a challenging task and relies heavily on effort of a multidisciplinary team, from treating hematologists to obstetricians. Individualized approach to manage these patients is essential, considering the gestational timing of presentation of ALL, cytogenetics, clinical profile, and active medical issues at diagnosis. Novel approaches used in our patients such as the use of modified BFM and E-WALL protocols, modifications with regard to timing of L-asparaginase administration, and antepartum use of rasburicase were met with favorable pregnancy outcomes.

Authors' Contributions

S.B. was involved in conceptualization, data collection, and manuscript drafting. S.G. helped in conceptualization, clinical data curation, and manuscript editing and analysis. S.S.R., S. Samanta, N.S. and S. Saha were involved in Institutional Medical Boards convened for patient management strategies. M.B. was involved in conceptualization, manuscript editing, analysis, and overall supervision.

Ethics Approval

Retrospective study

Consent for Publication

Yes.

Availability of Data and Material

Available for publication/review.

Funding

None declared.

Conflict of interest

None declared.

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Unusual Presentation of Wilms' Tumor in a 4-Month-Old Infant as Presternal Metastatic Swelling—A Case Report with Review of Literature

Md Fahim Ahmad[1] Prema Menon[1] Shailesh Solanki[1] Amita Trehan[2] Parikshaa Gupta[3]

[1] Department of Pediatric Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Pediatric Hemato-oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[3] Department of Cytology and Gynaecologic Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Prema Menon, MS, DNB, FRCS, MCh, FMAS, Department of Pediatric Surgery, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Room No. 3133, Level 3-A, Sector 12, Chandigarh 160012, India (e-mail: menonprema@hotmail.com).

Ind J Med Paediatr Oncol 2024;45:451–453.

Abstract

A 4-month-old infant presented with an enlarging large vascular presternal swelling noticed for the past 2 months. Clinical examination revealed a left renal mass in this otherwise asymptomatic child. She underwent left nephroureterectomy and excision of the skin metastasis following a course of chemotherapy. Preoperative cytology and postoperative histopathological examination confirmed Wilms' tumor with a single skin metastasis. We report this case for its rarity.

Keywords

- Wilms' tumor
- cutaneous metastasis
- presternal swelling
- anaplasia

Introduction

Wilms' tumor is the most common primary renal malignancy of childhood. It constitutes 6.3% of cases of childhood cancer and accounts for approximately 90% of all pediatric renal tumors.[1] Tumor usually arises from single kidney; however, there can be synchronous or multifocal tumors in around 10% of the patients and these usually tends to present at an earlier age. It is usually seen in children aged between 3 and 5 years and is unusual before 6 months of age.[2] The vast majority of patients presents with asymptomatic abdominal mass. In one-third of patients, there can be abdominal pain, hematuria, and hypertension. Rarely there can be atypical presentation because of compression of surrounding organs or infiltration into renal vein and inferior vena cava.[3] Lung is the most common site of metastasis followed by liver and contralateral kidney.[4] Cutaneous manifestations are not common in Wilms' tumor unlike other tumors like neuroblastoma, leukemia, rhabdoid tumor, and rhabdomyosarcoma that can present in early infancy with metastasis.[5]

In the index case, a 4-month-old infant presented with a presternal swelling and on further examination was found to have a left-sided flank mass. The diagnosis of Wilms' tumor with cutaneous metastasis was confirmed after further workup.

Case Report

A 4-month-old female child, first in birth order, born by full-term vaginal delivery, and asymptomatic at birth, was referred with a presternal swelling. This had been noticed since the age of 2 months by the parents and was gradually increasing in size. There was no history of loss of appetite or weight. She had normal bowel and bladder habits. There were no complaints other than the presence of the presternal swelling. An ultrasonography (USG) of the swelling done before referral was suggestive of hemangioma or arteriovenous malformation. On examination, a 6×4 cm, round, well defined, firm, nontender, noncompressible swelling was present over the presternal area with overlying darkened skin and few areas of ulceration and eschar (►**Fig. 1A**).

article published online
May 12, 2023

DOI https://doi.org/10.1055/s-0043-1766131.
ISSN 0971-5851.

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

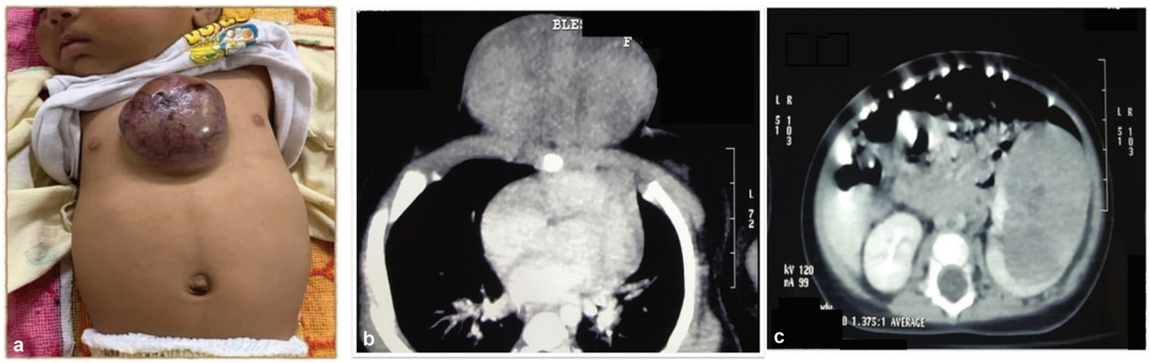

Fig. 1 (A) Single large skin metastasis in lower presternal area at presentation; (B) contrast-enhanced computed tomographic scan of chest shows a $3.8 \times 3.8 \times 6.3$ cm mass in the presternal area lying in subcutaneous plane with no intrathoracic extension; (C) contrast-enhanced computed tomographic scan of abdomen shows a $5.1 \times 3.8 \times 5.3$ cm hyperdense exophytic mass arising from the left kidney with no major vessel encasement or calcifications.

Incidentally, fullness was noted in the left flank region and on abdominal examination, a mass of size 4×5 cm was palpable in the left lumbar region that was firm, well defined, smooth, bimanually palpable, and nonballotable. She had no features of any syndrome associated with Wilms' tumor. USG abdomen revealed a hyperechoic 4×4 cm left renal mass. Contrast-enhanced computed tomography (CECT) chest showed that the presternal mass had no intrathoracic extension. (►**Fig. 1B**). CECT of abdomen showed a $5.1 \times 3.8 \times 5.3$ cm hyperdense exophytic mass arising from the left kidney with no major vessel encasement or calcifications (►**Fig. 1C**).

Fine-needle aspiration cytology smears from the left renal mass and chest wall swelling showed a predominantly dispersed population of blastemal cells with high nucleocytoplasmic ratio and hyperchromatic nuclei. Focal anaplasia and occasional mesenchymal fragments could also be noted. Cell blocks with immunohistochemistry were also suggestive of anaplastic Wilms' tumor with metastasis (►**Fig. 2**). Both the presternal swelling and renal mass showed a reduction in size after four cycles of age adjusted chemotherapy with doxorubicin, actinomycin D, and vincristine. The patient underwent left radical nephroureterectomy with lymph node sampling and excision of the chest wall lesion. Histopathological examination confirmed Wilms' tumor with lymph nodes free of tumor. Local staging was stage 1 as the tumor was fully excised and there was 99% necrosis. Margins of the local site tumor (abdomen) and metastatic site were also negative. After surgery, she developed surgical site infection that responded to antibiotics. The tumor was triphasic in nature and there was focal anaplasia on the initial biopsy that does not qualify for unfavorable histology. She therefore did not belong to poor risk histology and was planned for 27 weeks of chemotherapy with actinomycin D, doxorubicin, and vincristine. She defaulted after receiving 12 cycles of chemotherapy. The reason for abandonment of therapy is unclear. She expired 6 months after surgery at home after a brief period of complaint of fever, weight loss, and cough. The probable cause of death may be due to coronavirus disease 2019 or the malignancy itself.

Discussion

Wilms' tumor is the second most common childhood abdominal malignancy forming 6% of all the childhood cancers with a 5-year survival rate of nearly 90%.[1]

It usually presents as an asymptomatic abdominal mass. Other presentations include abdominal pain, fever, hematuria, hypertension, recurrent urinary tract infection, and anemia.[2,3] Metastasis occurs commonly in the lung, liver, and contralateral kidney. Less common sites include bone, skin, brain and orbit, and rarely testes.[4] Wilms' tumor is less frequent in infants with the mean age at diagnosis being around 8 months.[2] Complete surgical removal without tumor spillage is essential as these patients have sixfold increased risk of local abdominal relapse.[6] Because of refinement in risk stratification and advancement in chemotherapy, the overall survival has improved to greater than 90% for localized disease and 75% for metastatic disease.[7]

Unlike in older children, Wilms' tumor in infancy often has cystic appearance.[8] This cystic form is considered to be low-risk nephroblastoma, prognosis is better, and they may be treated with surgical resection alone.[9] Early detection is possible in specific syndromic associations if frequent checkups are done in the first year of life. In our case, the child presented at 4 months of age with cutaneous metastasis and features of anaplasia on cytological examination. Other more malignant tumors could be ruled out by immunohistochemistry of cell blocks, namely: malignant rhabdoid tumor kidney (as INI-1 retained), clear cell sarcoma kidney (cyclinD1 negative), neuroblastoma (chromogranin and synaptophysin negative), Ewing's sarcoma (CD99 negative), and lymphoma (leukocyte common antigen negative). The tumor cells were positive for vimentin and desmin.

Currently, tumor histology is considered as the most common "biomarker" reflecting prognosis. Anaplastic histology, especially diffuse anaplasia, is associated with higher recurrence rates, metastases, and death. The recommended National Wilms' Tumor Study group/Children's Oncology group chemotherapy protocols differentiate patients by presence and degree of anaplasia.[10,11]

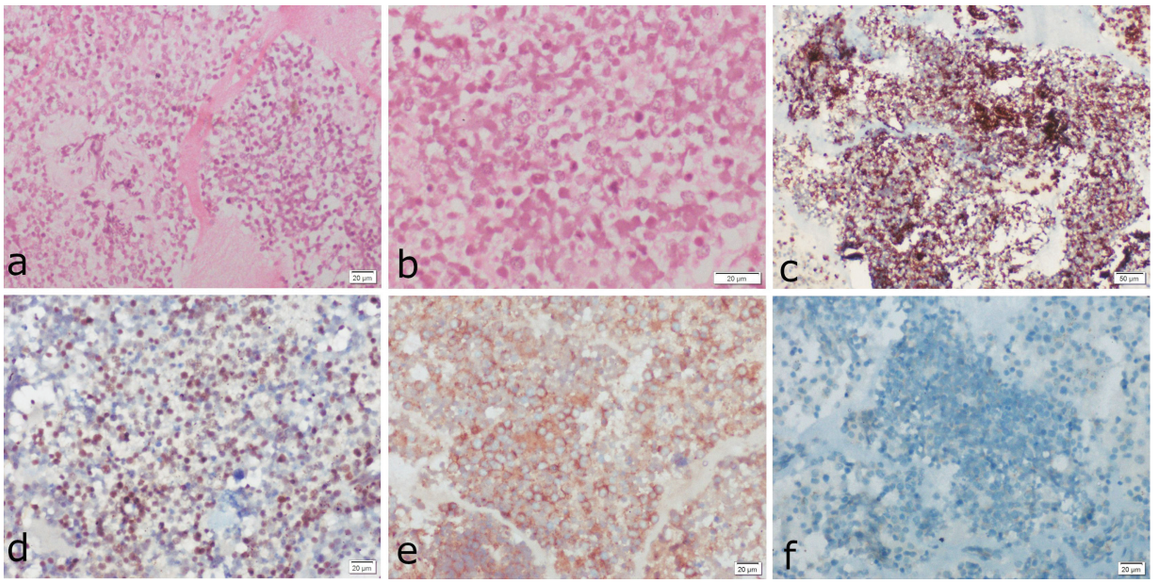

Fig. 2 (**A**, **B**) Sections from the cell block from the left renal mass and chest wall swelling showing a dispersed population and sheets of blastemal cells and occasional mesenchymal fragments (hematoxylin and eosin; **A**:20x, **B**:40x); (**C**–**F**) Immunocytochemistry for vimentin (**C**: 10x) shows diffuse strong positivity in the tumor cells, retained nuclear expression for INI-1 (**D**: 20x), and dot-like positivity for desmin (**E**: 20x). The tumor cells were negative for chromogranin, synaptophysin, WT1 (**F**: 20x), CD45, cyclinD1, and CD99.

On reviewing literature, we did not find any case of Wilms' tumor presenting as a single skin metastasis in an infant. We found one report of a 12-year-old child who had undergone nephrectomy 7 years back for Wilms' tumor, and presented with a lump in the parasternal area as a form of late recurrence.[12]

Conclusion

This case reveals an unusual presentation of Wilms' tumor in an infant that has not been reported before in literature. The child manifested first with a skin lesion at 2 months of age and on histopathological examination was revealed to have anaplastic Wilms' tumor, both of which are extremely rare.

Conflict of Interest

None declared.

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Paranasal Sinus Embryonal Rhabdomyosarcoma Metastasizing to Breast and Ovary on PET/CT—A Case Report with the Review of Literature

Vijay Singh[1] Vivek Saini[1] Manish Ora[1] Sanjay Gambhir[1]

[1] Department of Nuclear Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Ind J Med Paediatr Oncol 2024;45:454–458.

Address for correspondence Manish Ora, MBBS, MD, Department of Nuclear Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India- 226014 (e-mail: drmanishora@gmail.com).

Abstract

Rhabdomyosarcoma (RMS) is a malignant soft tissue tumor of skeletal muscle origin. The head and neck, urinary tract, and extremities are the common sites of origin. Embryonal, alveolar, pleomorphic, and spindle/sclerosing are subtypes. It is more common in childhood and rare among adults. The incidence and risk factors for this disease are mainly largely unknown. RMS is sporadic in most instances; however, it is attributed to familial syndromes in some situations—its metastasis to the lungs, bone marrow, and lymph nodes. Breast and ovary involvement is scarce. Diagnostic workup mainly includes contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI). However, ^{18}F-fluro-deoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) and PET/MRI are increasing contribution to providing functional insights about tumor biology and improving the diagnostic accuracy of the imaging workup. This report presents a case of the neck's embryonal RMS metastasizing simultaneously to the breast and ovary. PET/CT imaging revealed the unusual pattern, further validated by histopathology.

Keywords
- embryonal rhabdomyosarcoma
- metastasis
- breast
- ovary

Introduction

Rhabdomyosarcoma (RMS) is designated as the most frequently reported soft tissue sarcoma in children, accounting for more than 50% of soft tissue sarcomas. RMS can appear at any age, although 87% of patients present at an age younger than 15 years. It rarely affects adults.[1] Less than 1% of all malignancies are soft tissue sarcomas, and 3% of all soft tissue sarcomas are RMS.[2] It affects 4.3 cases per one million under 20 years of age annually.[2] RMS cells resemble skeletal muscle progenitor cells despite being derived from nonskeletal tissues.[3] RMS is divided into four clinical categories based on its histopathology—embryonal RMS (ERMS), alveolar RMS (ARMS), pleomorphic RMS (PRMS), and spindle cell and sclerosing RMS. ERMS accounts for most cases and has a favorable prognosis, but ARMS is clinically aggressive due to a propensity for metastasis and recurrence.[4] ERMS and ARMS are the most common histologies in children, but PRMS is nearly exclusively seen in adults. Furthermore, PRMS is more resistant to chemotherapy than ERMS and ARMS. RMS in older patients is associated with a poorer prognosis than in younger patients. They present with the primary tumor unfavorable and a more aggressive histologic subtype. Although the etiology and specific risk factors for RMS are unknown, in utero radiation exposure, faster in utero growth, low socioeconomic background, and parents who use recreational drugs during pregnancy all augment the chance of RMS. It usually presents as an isolated disease but has been linked to certain familial syndromes, including neurofibromatosis type I, Noonan syndrome, Li-Fraumeni syndrome (p53 mutations), Beckwith-Wiedemann syndrome, and Costello syndrome (HRAS mutations).[5]

article published online
April 28, 2023

DOI https://doi.org/10.1055/s-0043-1768179.
ISSN 0971-5851.

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

The location of the initial tumor, age at presentation, and metastatic disease influence the presenting signs and symptoms. The head and neck region, the genitourinary tract, and the extremities are common sites for origin. The tumor may originate in the orbit, para meningeal sites (middle ear, nasal cavity, paranasal sinuses, nasopharynx, infratemporal fossa), and other sites (scalp, parotid gland, oral cavity, pharynx, thyroid, and parathyroid glands). These tumors are most commonly ERMS and rarely spread to regional lymph nodes.[6] Genitourinary tract RMS mainly arises in the prostate and bladder. They present as hematuria, urinary tract infection, and features of obstruction. In females, the vagina, cervix, and uterus are common sites. Vaginal RMS mainly presents as bleeding or discharge per vaginum and is more common at a younger age, whereas uterine and cervical RMS is more common in older females.[7] The third most prevalent site of RMS is the extremities. These tumors usually appear as a painful lump or swelling with or without erythema of the surrounding skin in adolescents. The ARMS subtype accounts for about half of all extremities RMS.[6] The trunk, intrathoracic area, perineal–perianal region, and biliary system are less common sites. RMS most frequently metastasizes to the lung, followed by bone, bone marrow, and lymph nodes. Usually, 25% of the patients present with metastatic disease at the time of diagnosis. Visceral organ metastases are rare. There have been reports of primary RMS in the liver, brain, trachea, heart, and breast.[8]

Case Presentation

A 20-year-old female patient presented with a complaint of pain and swelling over the right side of the neck for 2 months. It was insidious in onset and progressively increased in size. She had swelling and bulging of the right eye and a diminution of vision for 1 month. On examination, she had multiple enlarged conglomerated lymph nodes over the right upper side of the neck and extending up to the posterior triangle of the neck. Contrast-enhanced computed tomography (CECT) of the head and neck was suggestive of a large, necrotic soft tissue mass lesion in the right maxillary, ethmoid, and sphenoid sinuses. It extended into the nasal cavity with the maxilla and cribriform plate erosion, and multiple cervical lymph nodes were also noted. Lymph node biopsy suggested ERMS. Immunohistochemistry (IHC) revealed tumor cells were positive for vimentin, desmin, Myogenin, and CD99 (paranuclear dot-like positivity) and negative for LCA, CD3, CD20, cytokeratin, synaptophysin, chromogranin, and terminal deoxynucleotidyl transferase. Ki67 index was approximately 50 to 60%. Baseline ^{18}F-fluro-deoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) could not be done due to the ongoing coronavirus disease 2019 pandemic. She was further treated with 20 gray/5 fractions (#) palliative radiotherapy (RT) to the orbit; post palliative RT, ^{18}F- FDG-PET/CT was performed. ^{18}F-FDG-PET/CT was performed intravenously after injecting 370 Megabecquerel (MBq) 18F-FDG (IV). Whole body PET/CT images were acquired 45 minutes after the FDG injection.

^{18}F-FDG-PET/CT revealed FDG avid soft tissue mass in the right paranasal sinuses (►**Fig. 1A**) eroding the medial wall of the orbit. Solitary skeletal metastasis was noted on the right iliac bone and multiple bilateral cervical lymph nodes. The patient received three cycles of vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy. Interim PET/CT showed a residual mass in the paranasal sinuses with cervical lymph nodes. Previously seen lesions showed partial treatment response (►**Fig. 1B**). She received three more

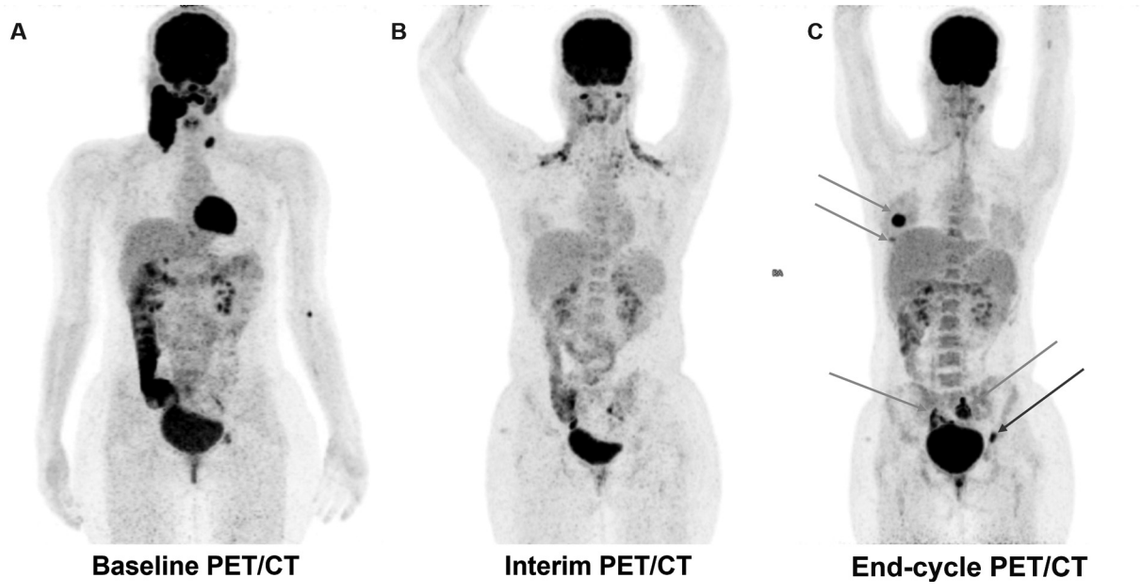

Fig. 1 Maximum intensity projection images of baseline positron emission tomography/computed tomography (PET/CT) reveal (**A**) flurodeoxyglucose (FDG) avid thickening involving paranasal sinus (PNS) and adjacent areas. Interim PET/CT (**B**) reveals no significant residual disease in the neck. End-cycle PET/CT (**C**) for treatment response reveals FDG avid metastatic involvement of right breast (red arrow), bilateral ovary (green arrow), and FDG avid lesion in left iliac bone (blue arrow).

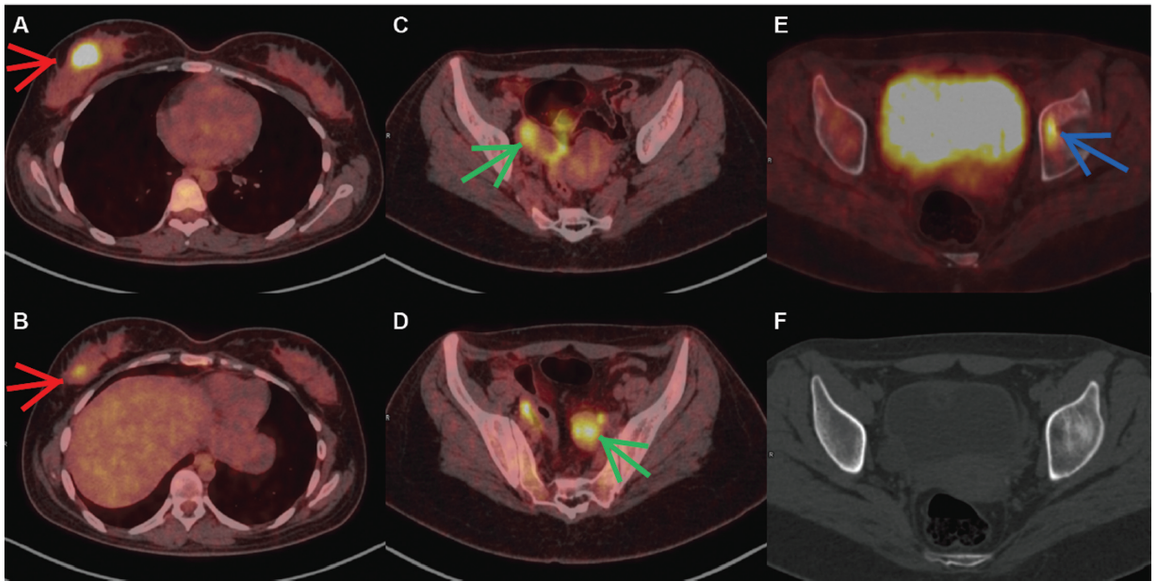

Fig. 2 End-cycle response positron emission tomography/computed tomography (PET/CT) fused images reveal flurodeoxyglucose (FDG) avid multiple lesions in the right breast (**A**, **B**); FDG avid lesions in the bilateral ovary (**C**, **D**), and FDG avid lesion in the left iliac bone (**E**) corresponding to axial CT image (**F**) reveal lytic lesions in the left iliac bone.

cycles of VAC chemotherapy and was referred for end-cycle PET/CT for treatment response. PET/CT revealed FDG avid and nonavid residual cervical lymph nodes. FDG avid soft lesions were noted in the right breast parenchyma and ovaries (►**Figs. 1C, –2A–D**). Also, metastatic lytic and sclerotic skeletal lesions were noted (►**Fig. 1C**, ►**Fig. 2**). The overall impression was suggestive of disease progression. Fine-needle aspiration cytology and histopathological examination (HPE) with immunohistochemistry suggested metastatic ERMS from both sites. The patient refused further treatment and was lost to follow-up.

Discussion

RMS is the most common soft tissue sarcoma in children. On the contrary, it is an uncommon neoplasm in adults and older population.[1] ERMS predominantly affects children in their first 5 years of life, but it may occur at older ages. ERMS typically occurs in and around the head, neck, bladder, vagina, prostate, and testicles. However, only a few primary cases are reported from the liver, brain, trachea, heart, and breast.[5] Two subtypes of ERMS are botryoid and spindle cell RMS. Sarcoma botryoides present as a grape-like lesion, particularly in the vagina or bladder. Botryoid and spindle cell RMS tends to have a better prognosis than conventional ERMS.

Lung, bone marrow, and lymph nodes are specific metastatic sites for RMS.[2] Metastasis to the breast and ovary is very rare. Our case, unfortunately, had HPE and IHC confirmed both breast and ovarian metastases. Breast metastases from RMS are exceptional, with an incidence of 6%.[9] Bilateral involvement is between 8 and 25%.[10] They occur mainly in adolescent girls, with the most primary tumors in the extremities.[9,10] The alveolar type has a strong connection with breast deposits. Breast metastases are believed to arise due to increased vascularity and rapidly growing mammary tissue at puberty.[9,10] Metastatic, as well as primary involvement of the ovary, is infrequent in RMS. We reviewed the literature for RMS metastasizing to the breast and ovary in the pediatric population (from age 0 to 18 years) and found 12 studies reporting breast metastasis, but ovarian metastasis was not reported (►**Table 1**). Out of 54 patients, only one was male, and the rest were female, demonstrating female predominance.

In most cases, the primary site was the extremity, followed by pelvic structures. Paranasal sinus as a site for primary was noted in eight (15%) cases. Out of 54 cases, 49 (90%) reported an alveolar variety of RMS; the embryonal variant was found in only a single case. Two studies showed the PET/CT utilization for metastasis detection and response evaluation. Most studies reported mortality in the follow-up period.

In our case, FDG-PET/CT revealed solitary skeletal metastasis in the baseline scan, and following chemotherapy, interim PET/CT revealed residual disease with partial treatment response. However, the patient developed further recurrence and ovarian breast metastasis demonstrated by FDG-PET/CT.

The diagnostic evaluation of a suspected RMS involves determining the primary disease extent and the presence of metastatic dissemination. A thorough physical examination should be carried out, with particular attention paid to the lymphatic structures in the region. A total blood count with differential, serum electrolytes, blood urea nitrogen, and liver function tests should be conducted along with serum creatinine, phosphorus, magnesium, uric acid, and calcium. Hypercalcemia due to bone absorption can develop in people with bone metastases, albeit uncommon. Bilateral bone

Table 1 Reported cases of rhabdomyosarcoma metastasis to the breast in the pediatric population ($n = 54$)

Sr no.	Authors (y)	No.	Age/sex	Primary site	Histology	PET	Outcome
1	Howarth[16] et al (1979)	6	11.5–16 F($n = 5$) M($n = 1$)	Extremity	Alveolar ($n = 6$) Mix ($n = 1$)	N	All died at 1–16 mo from breast metastasis
2	Bohman[17] et al (1982)	3	15–18 All F	Extremity, orbit, mandible	NA	N	NA
3	Copeland[18] et al (1985)	3	13–15 All F	Perineum	Alveolar	N	All died at 7–27 mo from diagnosis
4	Pettinato[19] et al (1989)	2	14–17 All F	NA.	Alveolar ($n = 1$) Embryonal ($n = 1$)	N	NA
5	Chan et al[20] (1991)	2	14–15 All F	Pelvis, perirectal	Alveolar	N	NA
6	Rogers et al[21] (1994)	2	12–16 All F	Perineum, extremity	Alveolar ($n = 1$) Primitive ($n = 1$)	N	All died of PD
7	Kwan et al[22] (1996)	2	14–15 All F	Extremity	Alveolar	N	Died with PD
8	Hays et al[23] (1997)	19	12–21 All F	Extremity ($n = 8$) Nasopharynx and paranasal sinus ($n = 7$) Trunk ($n = 4$)	Alveolar	N	Died with PD ($n = 3$) Alive with disease ($n = 3$) No evidence of disease ($n = 3$)
9	Vishnevskaia[24] et al (2004)	2	14 All F	Widespread metastasis	Alveolar	NA	Died within 3 mo–1.5 y
10	D'Angelo[25] et al (2010)	7	13-16 All F	Extremity ($n = 3$) vagina ($n = 1$) breast ($n = 1$) retroperitoneal ($n = 1$)	Alveolar	NA	All dead at 15–48 mo
11	Kebudi[26] et al (2017)	3	13–14/F	Extremity, perineum, sphenoid sinus	Alveolar	Y ($n = 3$)	Died with PD
12	Audino[27] et al (1995)	3	14–16 All F	Extremity	Alveolar	Y ($n = 3$)	Died($n = 1$) In remission($n = 2$)

Abbreviations: F, female; M, male; mo, month; *n*, number; N, no PET/CT done; NA, not available; PD, progressive disease; PET/CT, positron emission tomography/computed tomography; Y, PET/CT done.

marrow aspiration and iliac crest biopsies should be performed in the absence of abnormal peripheral blood counts or apparent bone metastases. Plain radiographs of the primary site and CT scans of the primary and adjacent structures should be done. Magnetic resonance imaging or ultrasonography helps determine the disease extent in malignancies of the extremity or head and neck region. ^{18}F-FDG-PET/CT can accurately detect tumor lesions extent and metabolic activity, aiding staging and evaluating therapy response in many malignant tumors. As a complement to staging, restaging, and response assessment of metastatic RMS, PET/CT imaging has steadily increased in use in the last decade.[11,12] HPE and IHC are necessary for confirming the diagnosis. In our case, FDG-PET/CT revealed solitary skeletal metastasis in the baseline scan. Interim PET/CT revealed residual disease with partial treatment response. However, the patient relapsed with unusual metastasis to the breast and ovary.

Treatment for RMS requires a multidisciplinary approach, including surgical excision with or without RT and chemotherapy. The prognosis of this disease depends upon the location of the metastatic burden and the treatment received[13] standard chemotherapy regimen in North America is VAC.[14] In Europe, the backbone consists of ifosfamide vincristine and actinomycin D.[14] A randomized trial showed no apparent difference in patient outcomes between the two treatment combinations.[14] VAC/IVA has remained the same chemotherapy regimen since it was developed four decades ago, despite changes in duration, dosage, and method of administration.[15] An open-label phase 3 trial (EpSSG RMS 2005) unambiguously showed that doxorubicin addition to the standard IVA backbone did not enhance patient

outcomes. Because of cardiotoxicity (especially in younger patients), there is a lack of rationale for its continued inclusion in the chemotherapy regimen. Disease progression is noted despite continuing a VAC-based chemotherapeutic regimen. Metastatic RMS has a poor prognosis. Multimodal chemotherapy, RT, mastectomy, and bilateral oophorectomy approaches depend on a patient's condition. Literature regarding the treatment protocol for such patients is very scarce.

Conclusion

RMS being a pediatric soft tissue sarcoma commonly metastasizes to lung, bone, and lymph nodes. The alveolar variety of RMS is more frequent than other types. Few cases of breast metastasis have been reported in the past; however, ovarian metastasis is not documented. We reported a rare case of ERMS metastasizing to the breast and ovary. This case also highlights the importance of the ^{18}F-FDG-PET/CT in the treatment response evaluation and disease monitoring.

Declaration of Patient Consent

The patient gave written consent; in the form the patient consents to have images and clinical information published. The patient acknowledges that his or her name or initials will not be publicized.

Conflict of Interest

None declared.

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Primary Renal Leiomyoma

Rashmi Joshi[1] Mayur Parkhi[2] Debajyoti Chatterjee[2] Girdhar S. Bora[3]

[1] Department of Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[3] Department of Urology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Debajyoti Chatterjee, MD, DM, Assistant Professor, Department of Histopathology, 5th Floor, Research Block A, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: devchat1984@gmail.com).

Ind J Med Paediatr Oncol 2024;45:459–460.

Sir,

Renal leiomyoma is a rare smooth muscle tumor accounting for 0.3% of all nephrectomies and 1.5% of all benign neoplasms.[1] They predominantly affect the female population between the second and fifth decades of life. Renal leiomyoma is predominantly asymptomatic and discovered incidentally on autopsy or when the patient is screened for some other symptoms. The most common presentations are abdominal mass, flank pain, and/or microscopic haematuria.[2] In the kidney, the lower pole is commonly involved. Leiomyomas are mostly subcapsular (53%) or capsular (37%), and these occur less often in the renal pelvis (10%) as these sites normally contain smooth muscles.[2] Macroscopically, these tumors are well circumscribed. The cut surfaces appear tan to white with a whorling pattern. Cystic degeneration is common.[3] Microscopically, long interlacing fascicles of spindle cells are seen. The presence of necrosis, atypia, or mitosis warrants the diagnosis of leiomyosarcoma and is hence looked for. Clinically, the important differential diagnosis includes renal cell carcinoma (RCC) and oncocytoma. Microscopically, stromal predominant angiomyolipoma (AML) also needs exclusion through thorough tissue sampling. Immunohistochemically, the diagnosis of leiomyoma is supported by diffuse smooth muscle actin (SMA) positivity and negativity for melanocytic markers (HMB45 and/or Melan-A). Both AML and oncocytoma are benign and require nephron-sparing surgery (NSS) like leiomyoma. However, RCCs are the most common outcome of contrast-enhancing renal mass and need elaborate management.[4] In the case of renal leiomyoma, the choice between partial and radical nephrectomy depends upon the tumor size and its location. There is no documentation of metastasis to date in the literature and most of the patients remain alive.[5]

A 56-year-old lady presented with a history of on and off right flank pain for 3 to 4 years. The pain was mild, dull aching and subsided on oral medication. There was no history of hematuria, burning micturition, or any previous significant past medical illness. She was hypertensive for 3 years with regular medication. On evaluation, the complete hemogram and renal and liver function tests were within normal limits. Contrast-enhanced computed tomography (CECT) showed a well-defined soft-tissue lesion measuring $3.6 \times 3.0 \times 3.1$ cm in the mid-pole cortex of the right kidney. On the noncontrast CT scan, the lesion appeared slightly hyperdense to isodense and showed plain CT attenuation of 33 to 46 HU. Furthermore, on the postcontrast scan, the lesion showed mild enhancement of up to 78 HU (maximum); however, it appeared hypodense with respect to renal parenchyma. The lesion showed a slight smooth exophytic bulge into overlying fat at the lateral aspect. Medially, the lesion appeared to merge with the mid-pole pelvicalyceal system. In addition, there was chronic calculous cholecystitis and uterine fibroid measuring 3.0×2.2 cm. A robot-assisted laparoscopic right NSS was performed. The specimen was sent for histopathological evaluation. Grossly, the right NSS specimen measured $4 \times 3.7 \times 2.5$ cm. An encapsulated solid tumor was seen measuring $3.6 \times 2.5 \times 2.6$ cm. The cut surface was homogenous, white, and firm with a whorling texture (►**Fig. 1A**). No areas of hemorrhage, necrosis, or calcification were noted. A peripheral rim of normal renal parenchyma was identified, measuring 0.3 cm. The histopathological sections showed a well-circumscribed tumor composed of smooth muscle cells arranged in long and short interlacing fascicles (►**Fig. 1B**). Additionally, individual tumor cells showed a mild degree of nuclear pleomorphism with spindle-shaped morphology and a moderate amount of eosinophilic cytoplasm. The nuclei appeared cigar shaped with both blunt ends, fine chromatin, and inconspicuous nucleoli (►**Fig. 1C**).

article published online
April 10, 2024

DOI https://doi.org/10.1055/s-0044-1785455.
ISSN 0971-5851.

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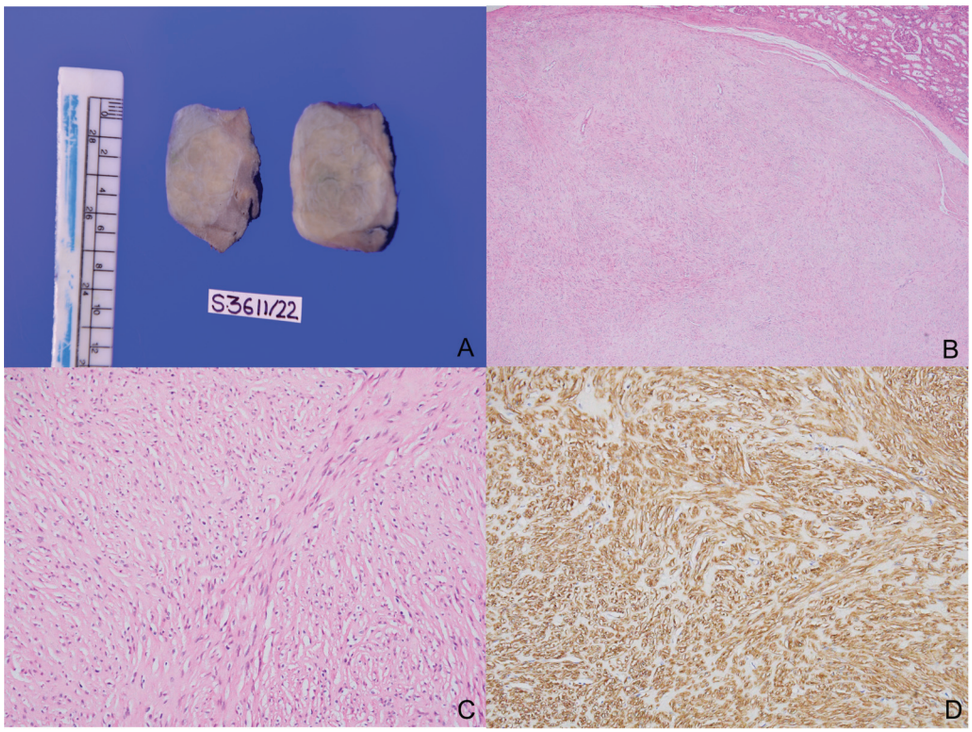

Fig. 1 (**A**) Gross specimen showing a well-circumscribed tumor. The tumor has tan to white color, rubbery texture, and whorled cut surface (scale bar = 2 cm). (**B**) The microphotograph showing a sharp demarcation from the surrounding normal renal parenchyma (hematoxylin and eosin [H&E]; ×100). (**C**) The tumor cells are arranged in intersecting fascicles (H&E; ×200). (**D**) Smooth muscle actin (SMA) immunohistochemistry shows diffuse strong positivity (×200).

Mitotic activity was infrequent (<1/10 hpf). No nuclear atypia, mitosis, or necrosis was seen. No perinephric fat extension was identified. On immunohistochemistry, the tumor cells exhibited diffuse cytoplasmic positivity for SMA (►**Fig. 1D**). Melan-A immunostain was negative. The Ki-67 proliferation index was less than 1%. The surgical resection margin was not involved. In view of morphology and immunohistochemistry, a diagnosis of leiomyoma (pT1a pNx; American Joint Committee on Cancer [AJCC] staging manual, 8th edition) was made. To the best of our knowledge, the association between renal and uterine leiomyomas was not found in the English literature. The patient is doing well after the surgery, and at the 1-year follow-up, she had no recurrence.

Author Contributions

R.J. and M.P. contributed to the analysis of the pathologic findings and manuscript writing. D.C. contributed to the pathologic analysis and manuscript editing. G.S.B. collected and critically analyzed the clinical data.

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

Ethics Statement

The authors obtained written informed consent for publication from the patient, and the manuscript as per the Institutional Ethics Committee requirements.

Funding

None.

Conflict of Interest

None declared.

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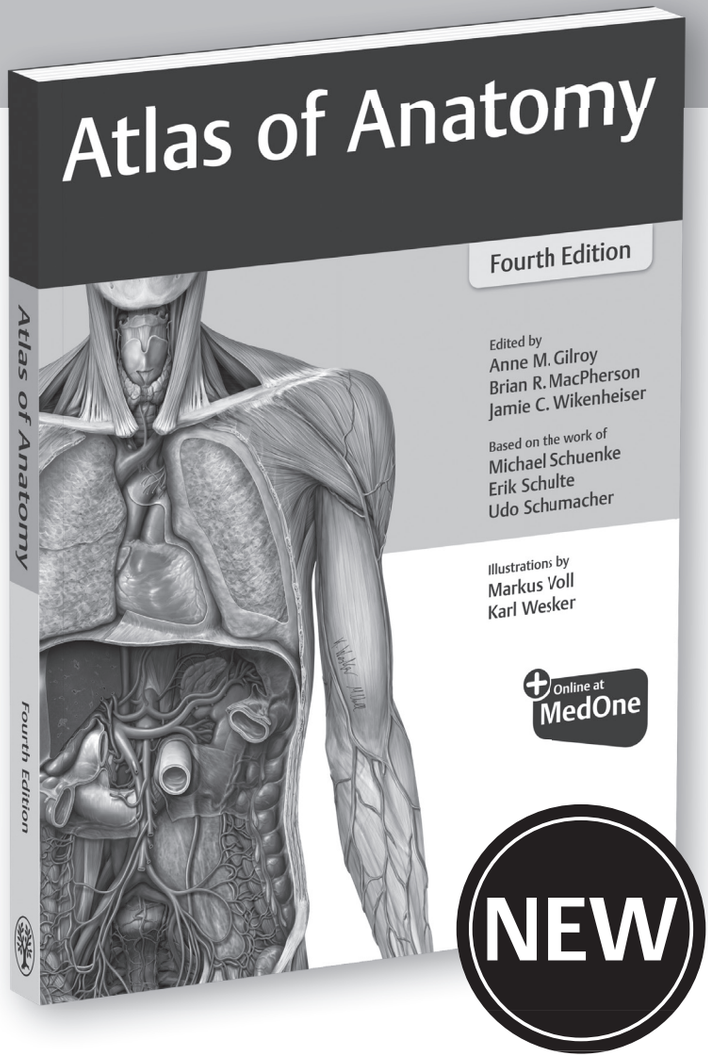

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