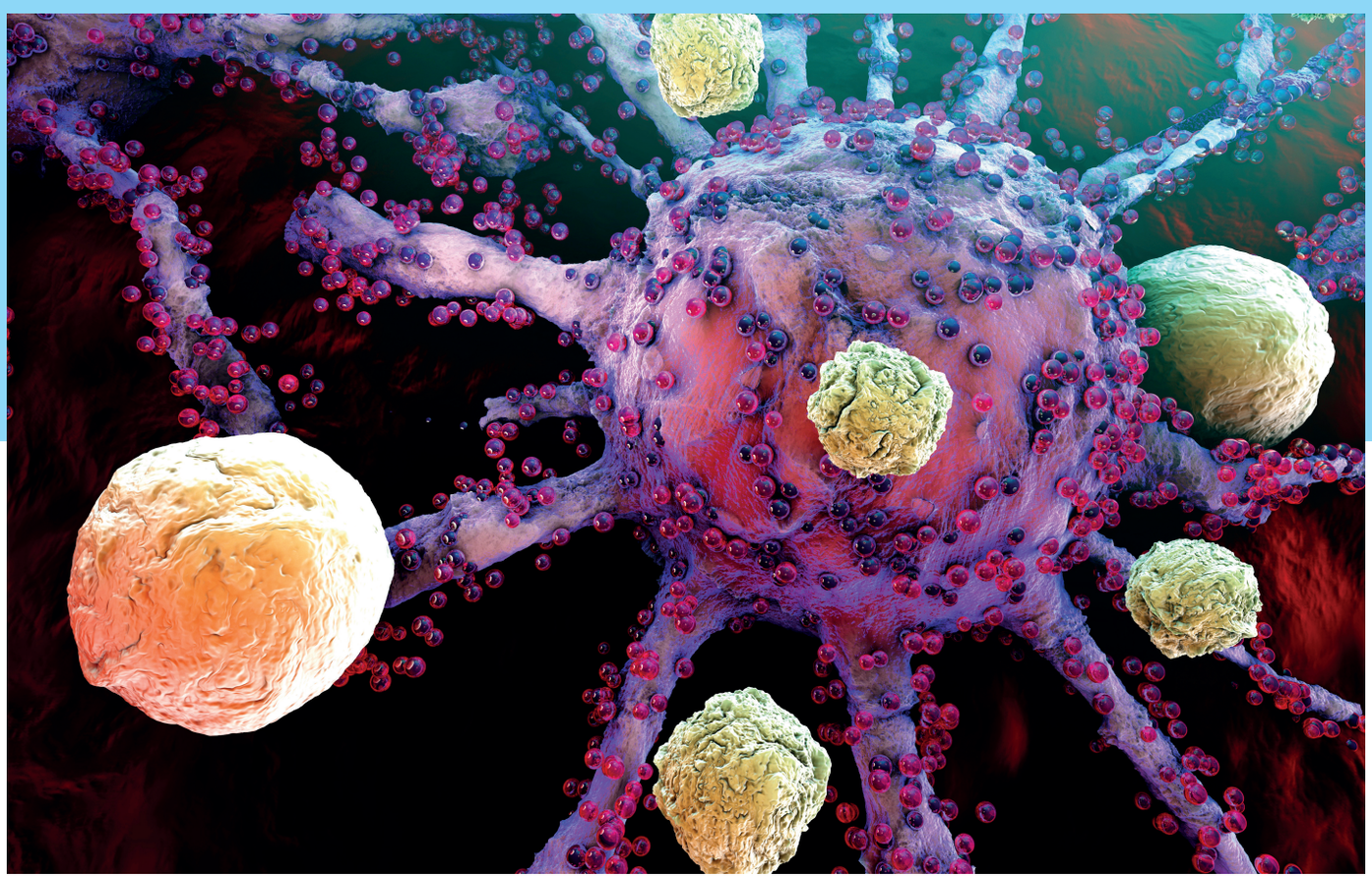
ISSN 0971-5851
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

Number 2 • Volume 45 • Pages 95–198 • April 2024



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eISSN 0975-2129

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.

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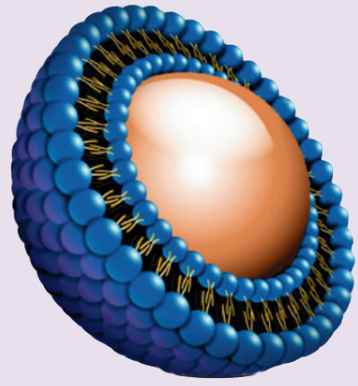

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Therapy for Recurrent High-Grade Epithelial Ovarian Cancer—The Current Status and Future Trends

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Ind J Med Paediatr Oncol 2024;45:95–105.

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Abstract

Ovarian malignancy is the seventh most frequently diagnosed cancer among women. The most common type is epithelial ovarian cancer. Several subtypes with distinct biological and molecular properties exist, and there is inconsistency in availability of and access to different modalities of treatment. The standard first-line management is combining surgery and platinum-based chemotherapy. Most of them are diagnosed at an advanced stage due to which they have poor outcomes. The existing screening tests have a low predictive value. Even with the best available upfront treatment, high rates of recurrences are observed. As a result, there have been major advances in the treatment of recurrences with the development of anti-angiogenic agents and PARP inhibitors. It has led to the improvement in survival and quality of life among the relapsed epithelial ovarian cancers. This review is focused on the management of recurrent epithelial ovarian cancers and future directions based on current evidence. The application of a personalized and structured approach will meaningfully bring changes in the paradigm of care in these groups of patients.

Keywords

- epithelial ovarian cancer
- recurrent
- chemotherapy
- targeted therapy

Introduction

The newly diagnosed advanced epithelial ovarian cancer (EOC) is typically treated in the frontline setting by combining cytoreductive surgery and doublet chemotherapy, which is routinely paclitaxel and carboplatin.[1] Most of the women experience good responses, which includes complete responses to neoadjuvant chemotherapy, but disease recurrences are not uncommon.[2]

The indicators which influence prognosis of recurrent EOCs include Eastern Cooperative Oncology Group (ECOG) performance status, tumor volume, histology, and platinum-free interval (PFI).

PFI is defined as the time from last platinum treatment to recurrence and is the basis for rechallenge of platinum-based chemotherapy.[3] The classification was specified at the fourth Vancouver Ovarian Cancer Consensus Conference in 2010 which divided recurrent EOCs into four categories[4]:

a. PFI <1 month—platinum refractory.
b. PFI 1 month to 6 months—platinum resistant.
c. PFI 6 months to 12 months—partially platinum sensitive.
d. PFI >12 months—Platinum sensitive.

This review focuses on the current standards and choices of therapy available in recurrent ovarian cancers (ROCs) and a discussion on future trends.

Methods

We identified articles on PubMed in the past 10 years with keywords "recurrent," "epithelial ovarian cancer," "chemotherapy," "targeted therapy" published in English language as

article published online September 29, 2022

DOI https://doi.org/10.1055/s-0042-1742321.
ISSN 0971-5851.

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

randomized controlled trials or systematic review. The articles related to management of recurrent high-grade serous and epithelial carcinomas were included and rest were excluded. The most recent articles were given more value to keep the review as up to date as possible. Of the results, 100 relevant articles were taken for preparation for this review after excluding the irrelevant articles, duplicated articles, and articles which were published only as an abstract. We also identified some relevant articles within the articles that were picked from the above search which were pertinent to the topic.

Mechanisms of Resistance to Platinum Compounds

There are several mechanisms of cellular resistance to platinum compounds that have been described in various in vivo and in vitro studies. These mechanisms can be classified in two groups:[5,6]

1. Those that limit the generation of cytotoxic platinum-deoxyribonucleotide (DNA) adducts.
2. Those that avert cell death that occurs following platinum-DNA adduct formation.

Six DNA repair pathways are involved in maintenance of cellular machinery. These are mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), non-homologous end joining, and Fanconi Anemia (FA).[6]

NER defects are associated with an exceptional sensitivity to platinum compounds whereas defects of MMR correlate with resistance to the latter.[7] BER has little evidence linked to the repair system of platinum containing drugs. Cells deficient in HR and FA have been shown to be extremely sensitive to platinum agents as these pathways are linked to the cellular response to platinum agents.[8] Other proteins and pathways participating in the DNA damage response that have been involved with the activity of platinum agents are ATR and ATM proteins and checkpoint proteins, CHK1 and CHK2.[9] The DNA repair gene, CDK12 (also known as the master regulator) modulates sensitivity to PARP inhibitors and platinum agents.[10]

The molecular characterization of EOC has unveiled that more than 50% of high-grade serous ovarian cancers have HR repair deficiency due to either germline or somatic mutations, promoter hypermethylation in BRCA1, BRCA2, and RAD51C, and mutations in FA and RAD genes which may determine the extreme sensitivity to platinum agents.[6]

Higher levels of ERCC1/XPF complex have been ascertained in ovarian cancer patient xenografts that have been made resistant in vivo to cisplatin. However, these data need to be authenticated in a larger cohort of patients with platinum-resistant tumors to draw stronger conclusions.[7]

An enhanced awareness of the molecular basis of platinum resistance may lead to the development of novel antitumor approaches that will sensitize unresponsive ovarian cancers to platinum-based chemotherapy. Various two-dimensional human and murine ovarian cancer cell lines, and patient-derived xenografts (PDXs), have been developed in this regard.[6] The use of organoids derived from distinct tumor types has been suggested as an intermediary tool between 2D cultures and PDXs. They maintain important characteristics of the tumors they arise from along with infiltrating cells.[11]

Primary Therapy

Platinum-Resistant Recurrence

Chemotherapeutic Agents

Platinum-resistant recurrences confer a poor prognosis. They have a chemotherapy response rate of approximately 10 to 15%, with a progression-free survival (PFS) less than 4 months and an overall survival (OS) time of approximately 1 year.[12] Therefore, chemotherapy for platinum-resistant ROC is considered as palliative and currently monotherapy is recommended over multidrug chemotherapy. The agents that are commonly used include liposomal doxorubicin (PLD), paclitaxel, topotecan, or gemcitabine.[13] The choice of drug is mainly dependent on the toxicity profile, the deleterious effects of previous therapy, and the patient's desire.

Two phase 3 trials have compared gemcitabine and PLD.[14,15] A systematic review of these trials revealed no difference in survival but different and comparable adverse events.[16] Six studies comparing topotecan with various agents like PLD and paclitaxel also revealed similar results but with increased rates of toxicity.[17] Several non-platinum agents have been tried as doublets, but none have revealed a significant improvement in survival and yielded increased rates of toxicities. Oral metronomic therapy with cyclophosphamide, etoposide, hormonal agents, and tyrosine kinase inhibitors like pazopanib have been evaluated in various retrospective studies with encouraging results.[18–20]

Targeted Agents

Anti-vascular endothelial growth factor (VEGF) agents redistribute the circulation in tumoral tissue, and increase the overall delivery of chemotherapy and oxygen in tumor tissue. This explains its greater efficacy when combined with chemotherapy. The PLD or taxanes combinations with bevacizumab are the most active and commonly used agents.[21]

The AURELIA trial, which investigated the addition of bevacizumab to single-agent chemotherapy in platinum-resistant ROCs, indicated that the median PFS and overall response rate (ORR) were significantly longer in patients receiving the combination (PFS-6.7 months vs. PFS-3.4 months, $p = 0.001$).[22] A recent update of this study reported a more pronounced effect on OS in the taxane cohort (HR 0.65, 95% CI 0.42–1.02), presumably due to the synergistic antiangiogenic activity of the two agents.[23]

Platinum Sensitive Recurrence

In the platinum sensitive recurrences, a complete response to chemotherapy ranges between 15 to 30% with an overall

response between 30 to 70%. This benefit has a positive correlation with the length PFI.[24]

The frequently used platinum agent is carboplatin and is used in combination with PLD, paclitaxel, or gemcitabine. A pooled analysis of three phase 3 trials of Arbeitsgemeinschaft Gyna kologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and International Collaborative Ovarian Neoplasm collaborators showed a significant improvement in PFS (HR, 0.76; 95% CI, 0.66–0.89; $p = 0.0004$) and OS (HR, 0.82; 95% CI, 0.69–0.97; $p = 0.02$) in platinum-sensitive ROC treated with platinum–paclitaxel combination versus single-agent platinum.[25] A phase 3 trial showed that the combination of gemcitabine and carboplatin had a significantly improved PFS versus single agent carboplatin (HR, 0.72; 95% CI, 0.58–0.90; $p = 0.0031$).[26] The CALYPSO trial showed that the carboplatin and PLD combination had a statistically significant improvement in PFS over paclitaxel and carboplatin (HR, 0.82; $p = 0.005$) with lowering of toxicities including carboplatin hypersensitivity reactions.[2]

In case of further recurrences in more than 6 months, platinum-based combined chemotherapy regimen can be utilized, based on PFI. But at subsequent recurrences the platinum sensitivity abbreviates.[27]

Toxicities to Chemotherapy

A detailed history of previous chemotherapy and toxicities is essential for a decision on the choice of chemotherapy. Residual neuropathy is important before rechallenging a taxane. The possibility of hypersensitivity to carboplatin is always present when used in the recurrent setting. This risk increases with subsequent cycles with inclusion of a carboplatin. The exact mechanism of this toxicity is unknown. Common hematological toxicities include thrombocytopenia and anemia which can occur with any of the agents. Other non-hematological toxicities include chemotherapy induced nausea and vomiting, myalgias, fatigue, etc.

Targeted Agents

The trials that investigated the role of bevacizumab in platinum-sensitive ROC were the OCEANS and GOG-213.

The OCEANS trial was conducted among 484 patients who were randomized to the standard chemotherapy with placebo or to standard chemotherapy and 3-weekly bevacizumab (15 mg/kg) followed by maintenance until progression of disease or intolerable toxicity. Median PFS (12.4 vs. 8.4 months) and ORR (78.5 vs. 57%) was significantly higher among the bevacizumab group with acceptable toxicity profile.[28] However, this trial failed to prove an OS advantage in the recently updated report (33.6 vs. 32.9 months; $p = 0.65$).[29]

The GOG 213 trial randomized 674 patients of platinum sensitive ROC to a combination of carboplatin with paclitaxel with or without bevacizumab and maintenance bevacizumab which was continued until disease progression or impermissible toxicity. The results showed an improvement in the PFS and median OS in the bevacizumab group with acceptable toxicity profile.[30]

In the ICON 6 trial, platinum sensitive ROC patients were randomized to three cohorts: platinum-based chemotherapy alone, platinum-based chemotherapy with cediranib followed by maintenance placebo, or platinum-based chemotherapy plus cediranib followed by cediranib maintenance. The cediranib maintenance arm showed a significant enhancement in PFS when compared with chemotherapy alone but with added toxicities. The OS data are still immature.[31]

The MITO16/MaNGO-OV2B study evaluated the use of bevacizumab beyond progression in platinum sensitive ROC. Four hundred and five subjects, previously treated with bevacizumab, were incorporated into the study. The analysis was done at a median follow-up period of 20.3 months; the median PFS was 8.8 months in the chemotherapy set and 11.8 months in the bevacizumab plus chemotherapy group and the results reached statistical significance. The OS data are immature. The adverse effects were manageable and included thrombocytopenia, hypertension, and proteinuria.[32]

Partially Platinum Sensitive Recurrence

Most of the trials of platinum sensitive recurrence included patient groups recurring at more than 6 months interval. But the group recurring at 6 to 12 months represents a special group with characteristics linking platinum sensitive and platinum resistant recurrences. This cohort demonstrates discouraging response rates and survival to rechallenge of platinum-based therapy as compared with those recurring >12 months from previous platinum therapy. They are mostly treated in lines of platinum sensitive recurrences with addition of anti-angiogenic agents.

There have been attempts to extend PFI to more than 12 months. The MITO-8 trial randomized subjects of partially platinum sensitive ROC to either non-platinum chemotherapy followed by platinum chemotherapy at subsequent recurrence (experimental arm) or platinum-based chemotherapy followed by non-platinum chemotherapy at subsequent recurrence. No OS benefit was noted, and both PFS and quality of life worsened in the set of patients receiving non-platinum therapy at the first instance.[3]

Maintenance Therapy

Multiple trials and reviews have analyzed the utilization of maintenance therapy in ROCs after the primary treatment in the recurrent setting for improvement of durability in the second remission. The main goals of maintenance treatment are to lengthen survival meaningfully and extend the period between subsequent treatment lines, thus allowing patients to avoid the unwanted chemo toxicities that can adversely affect their quality of life.[33] Maintenance therapy may be distinguished into two types:

1. Introduction of a new therapy after a patient achieves a response to primary chemotherapy (switch maintenance).
2. Continual administration of a drug that was used in combination with chemotherapy (continuation maintenance).[34]

As detailed earlier, the OCEANS and GOG 0213 trial (platinum sensitive), AURELIA (platinum resistant) which

evaluated maintenance bevacizumab and ICON 6 (platinum sensitive) with maintenance cediranib in platinum sensitive ovarian cancers showed PFS benefit.[28–31] ►**Table 1** recapitulates the role of antiangiogenic maintenance in ROCs.

The dose of bevacizumab used in clinical trials and that has been approved is 15 mg/kg. Only trial to use a different dose is the ICON 7 trial which used 7.5 mg/kg every 3 weeks. Recently an expert panel from India has recommended the use of 7.5 mg/kg in ovarian cancers considering the practicality in clinical use.[35]

PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) represent one of the most promising agents in the treatment of ovarian malignancy. The PARPi act on the principle of synthetic lethality. Synthetic lethality is where disarray of one gene is compatible with cell viability; however, simultaneous loss of both the genes results in cell death. These compounds compete with nicotinamide for the active site of PARP enzyme which is essential for the repair of single strand breaks[36] (mainly the PARP 1 and to a lesser extent PARP 2 and PARP 3). They are efficacious against HR repair deficient tumors. Since BRCA1/2 mutated tumor cells have hampered HR activity, they are used in the treatment of BRCA mutant breast, ovarian, pancreatic, and prostate cancers.[37] Further details on the mechanism of action of PARPi are beyond the scope of this review.

The approximate prevalence of BRCA1/2 mutation in patients with high-grade serous ovarian cancers is 20 to 25% and might be higher in patients with platinum-sensitive, ROC.[38–40] Several PARPi have been used in various clinical settings. The commonly used molecules include olaparib, rucaparib, niraparib and the newer ones are veliparib and talazoparib.

The SOLO2, which was a phase 3 trial of olaparib maintenance therapy in platinum-sensitive ROCs in subjects harboring germline BRCA mutations, showed a statistically significant improvement in PFS for olaparib maintenance versus placebo (19.1 vs. 5.5 months, HR = 0.30; $p < 0.001$).[41]

In the NOVA trial with niraparib in platinum sensitive ROC, the PFS in patients harboring germline BRCA mutations was significantly improved when compared with placebo (21.0 vs. 5.5 m). The more interesting fact of this trial was that there was sustained PFS benefit in the non-germline BRCA subjects and those without HR deficiency (9.3 vs. 3.9 months) indicating a possible utility for patients when used as a maintenance in platinum sensitive settings irrespective of mutational status.[42]

Lastly, in the ARIEL3 trial, rucaparib maintenance therapy significantly ameliorated the median investigator-assessed PFS versus placebo in all cohorts of patients with platinum sensitive ROCs (16.6 vs. 5.4 months; hazard ratio 0·23 [95% CI 0.16–0.34]; $p < 0.0001$).[43]

The adverse event profiles of PARPi as maintenance treatment in the recurrent setting are similar. Most of them are low grade (grade 1 or 2) and manageable with supportive care or dose modification. Hematologic adverse events are considered as a class effect of PARP inhibitors, most common being anemia. The most common non hematologic adverse events associated with PARPi are gastrointestinal side effects. There have been occurrences of myelodysplastic syndrome or acute myeloid leukemia, but the incidence seems to be low.[41–43]

►**Table 2** summarizes the PARPi in platinum sensitive ROC.

Endocrine Therapy

The Ovarian Cancer Tissue Consortium Study established that high-grade and low-grade serous ovarian carcinomas, and endometrioid variants express maximum levels of estrogen receptors.[44] Various trials of endocrine therapy in EOC have shown response rates ranging from 10 to 15% and disease stabilization rates between 30 and 40% as detailed in various systematic reviews and meta-analyses.[45,46] Even though both tamoxifen and aromatase inhibitors have been studied in various retrospective studies, none have yielded encouraging results. Moreover phase 3 studies are lacking introspection on this aspect. As such,

Table 1 Anti angiogenic agents in recurrent ovarian cancers

Trial	Experimental arm	Response rates (%)	Median PFS
OCEANS[28] (platinum sensitive)	Carboplatin AUC 4 plus gemcitabine 1,000 mg/m^2/d on every 21 d plus bevacizumab 15 mg/kg followed by bevacizumab maintenance.	78.5 vs. 57.4 $p < 0.001$	12.4 vs. 8.4 mo HR, 0.484 (95% CI, 0.388–0.605) $p < 0.001$
GOG 213[30] (platinum sensitive)	Carboplatin AUC 5 plus paclitaxel 175 mg/m^2 plus bevacizumab 15 mg/kg every 21 d followed by maintenance of bevacizumab.	78 vs. 59 $p < 0.001$	13.8 vs. 10.4 mo HR, 0.628 (95% CI, 0.534–0.739) $p < 0.001$
ICON 6[31] (platinum sensitive)	Cediranib in combination with platinum-based chemotherapy followed by maintenance of cediranib.	–	11.0 vs. 8.7 mo HR 0·56 (95% CI, 0.44–0.72) $p < 0·0001$
AURELIA[22] (platinum resistant)	Bevacizumab to single-agent chemotherapy.	27.3 vs. 11.8	6.7 vs. 3.4 mo HR 0.48 (95% CI, 0.38–0.60; $p < 0$ 0.001

Abbreviations: AUC, Area under the curve; HR, Hazard ratio; CI, Confidence Interval.

Table 2 PARP inhibitors in recurrent platinum sensitive ovarian cancers

Agent	Trial	Arms	Results
Olaparib	SOLO2[41]	Arm 1: Placebo maintenance Arm 2: Olaparib 300 mg bd maintenance	PFS Arm 2–19.1 m PFS Arm 1–5.5 m Updated OS HR 0.74 in favor of Olaparib (median follow-up: 65 mo)
Niraparib	NOVA[42]	Arm 1: placebo maintenance Arm 2: niraparib 300 mg q d	Arm 1: gBRCA +: 5.5 gBRCA −, HRD +: 3.8 gBRCA −, HRD −: 3.9 Arm 2: gBRCA +: 21.0 gBRCA −, HRD +: 12.9 gBRCA −, HRD −: 9.3
Rucaparib	ARIEL 3[43]	Arm 1: placebo maintenance Arm 2: rucaparib 600 mg bid	Arm 1: gBRCA +: 5.4 HRD +: 5.4 Intention to treat: 5.4 Arm 2: BRCA +: 16.6 HRD +: 13.6 Intention to treat: 10.8

Abbreviations: PARP, Poly (ADP-ribose) Polymerase; PFS, Progression Free Survival; gBRCA, Germline BRCA; HRD, Homologoud recombinant Deficient.

endocrine therapy is not considered a standard of care and its use is not consistent worldwide. But in clinics many clinicians find it as a good alternative in relapsed cases in view of its ease of administration, favorable toxicity profile, and inexpensiveness. Patients with an estrogen receptor histoscore >200 (calculated as the percentage of tumor cells stained and intensity of the stain) and a treatment free interval of 180 days are most likely to derive benefit.[47]

Surgery

The role of secondary cytoreductive surgery (SCS) is a controversial area which still needs further research. Two trials have investigated this aspect of ROC. The GOG 213 trial conducted in platinum sensitive ROC had an arm randomized to SCS and did not show an improvement in median OS with SCS followed by chemotherapy compared with chemotherapy alone (50.6 vs. 64.7 months, respectively).[48] On the other hand, the results of AGO DESKTOP III/ENGOT ov20 trial which was recently presented, demonstrated a significant improvement in median OS of 7.5 months in the SCS followed by chemotherapy arm compared with the chemotherapy-alone group (53.7 vs. 46.2 months, respectively).[49] A positive AGO-score is based on PS ECOG 0, ascites ≤500 mL, and complete resection at initial surgery. One of the main reasons quoted as the reason for this difference were selection criteria or surgical techniques. The most recent SOC 1 trial conducted in China at multiple centers in the platinum sensitive ROCs showed that the median PFS was 17.4 months in the surgery group and 11.9 months in the no surgery group (HR 0·58; 95% CI 0.45–0.74; p <0·0001). The OS data are still immature to draw further conclusions on the trial results.[50]

Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is being increasingly used in the first-line setting along with primary cytoreductive surgery. Trials are ongoing to evaluate its role in secondary and further recurrences, although further evidence is required. Many retrospective studies have pointed toward a role of HIPEC in the recurrent setting.[51,52]

Future Directions

As detailed earlier, most patients with advanced ovarian malignancies eventually progress to develop recurrences that are chemotherapy resistant. Novel methods to the diagnosis and treatment are, therefore, urgently needed to improve the current standards of care.

Recent advances in molecular characterization have revealed that EOC can be classified into two distinct groups termed type I and type II carcinomas.[53,54] This aids in more definitive depiction of disease and prediction of patient prognosis. This provides insight into the mechanisms cardinal to the evolution of EOCs.[55] The classification is provided in ►**Fig. 1**.

The Cancer Genome Atlas (TCGA) has identified that around 96% of high-grade serous ovarian cancer is characterized by TP53 mutations; low prevalence but statistically frequent somatic mutations in nine genes including NF1, BRCA1, BRCA2, RB1, and CDK12. The various pathways altered in serous ovarian cancers are RB and PI3K/RAS pathways, NOTCH pathway, genesis in the HR pathway, and FOXM1 transcription pathway network. Four subtypes were identified based on gene content—immunoreactive, differentiated, proliferative, and mesenchymal.[38] The clinical significance of this classification is yet to be utilized in clinical practice.

In yet another classification, the serous ovarian cancers have been divided into four classes in relation to DNA repair,[56] after the introduction of PARP inhibitors:

1. Women having a germline mutation in *BRCA1*/2 or other DNA repair-related genes.
2. Tumors having somatic mutations in the DNA repair genes.
3. Homologous recombinant-deficient tumors.
4. Those without identifiable DNA repair defects.

Various chemosensitivity and resistance assays (chemoresponse assays) have been used to interrogate the complex biology of EOC. Initially, two 2D culture systems, MiCK assay (based on the principle of drug-induced apoptosis) and ChemoFx assays (live cells quantified microscopically using automated cell-counting software) were commercially tested. At present, 3D culturing techniques, in which cells are able to interact with each other and with the ECM to form organoids or spheroids, are being widely adopted in drug screening and toxicity assays. These are rich in cancer stem cells, which in their natural tumor microenvironment can be studied for disease progression, metastasis, and chemotherapy resistance. These assays need to be validated through well-designed prospective and blinded multicenter clinical trials for further use in clinical practice.[57]

Newer Therapies

The combination of PARPi, niraparib, and the anti VEGF agent, bevacizumab has been tried in platinum sensitive ROC in the phase 2 AVANOVA trial. Ninety-seven patients were enrolled and randomly assigned to the treatment. At a median follow-up of 16.9 months, the combination significantly improved the PFS (11.9 months [95% CI 8.5–16.7] vs. 5.5 months [3.8–6.3]).[58] The updated analysis continued to reinforce the preliminary results, with 66% reduction in the risk of progression of disease or death (HR, 0.34; 95% CI, 0.21–0.54). The median PFS in the bevacizumab arm was 12.5 months versus 5.5 months with niraparib alone arm.[59] Further phase 3 trials are required for drawing a definitive conclusion. A phase 3 ICON 9 trial which is evaluating the combination of olaparib and cediranib (both oral agents; hence the convenience of administration) in platinum sensitive ROC is recruiting to answer this question.

The SOLO 3 trial which compared olaparib and PLD in BRCA mutant platinum sensitive ROC after two prior lines of therapy resulted in statistically significant and clinically relevant improvement in ORR and PFS in favor of olaparib (median PFS 13.4 vs. 9.2 months, HR 0.62 [95% CI, 0.43–0.91]).[60]

Mirvetuximab Soravtansine, an antibody–drug conjugate (ADC) comprising a humanized anti-folate receptor α (FRα) monoclonal antibody, has been tried in platinum-resistant ROC. Although the initial phase 2 trials were encouraging, the phase 3 FORWARD 1 trial failed to meet its primary end

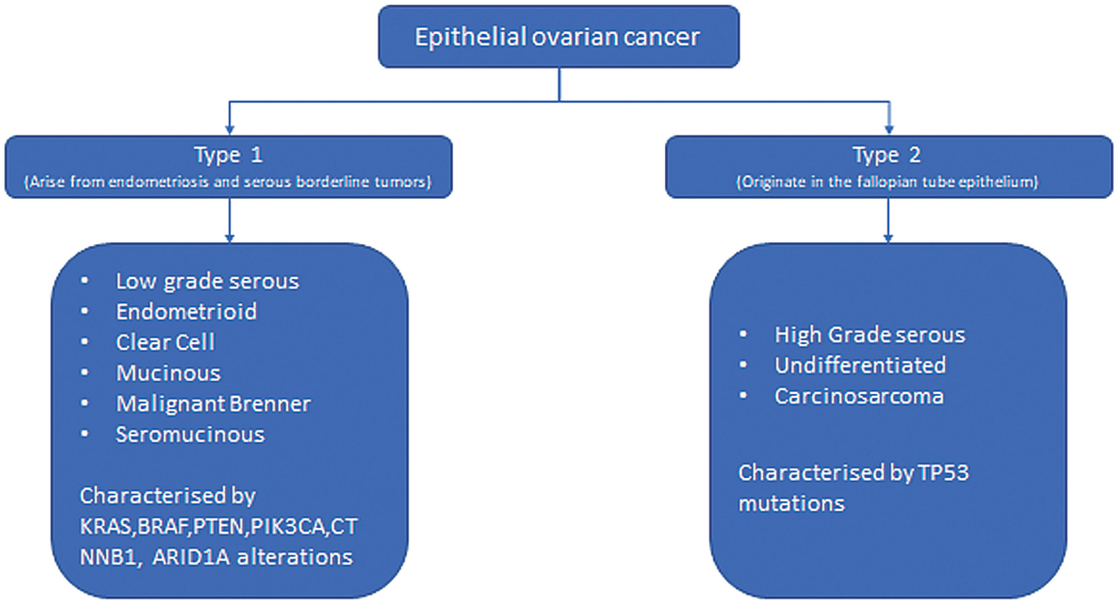

Fig. 1 Dualistic model of ovarian carcinogenesis.

point of PFS.[61] Currently, the combination of this ADC with bevacizumab is being tried in clinical trials. The phase 1b trial has shown good efficacy and tolerability to this combination.[62] Other molecules targeting FRα like vintafolide, farletuzumab had shown initial promise but failed to show significant benefits in phase 3 trials.

In a phase 2 trial, the WEE1 inhibitor, adavosertib, combined with gemcitabine was attempted in platinum resistant and refractory ovarian cancers. The combination yielded improved PFS (median PFS 4.6 months [95% CI 3.6–6.4] with adavosertib plus gemcitabine vs. 3.0 months [1.8–3.8] with placebo plus gemcitabine) which was statistically significant.[63] ATR inhibitor, berzosertib combined with gemcitabine, has been tried in a phase 2 trial and has shown improvement in PFS but warrants further investigation.[64]

Immunotherapeutic agents have also been tried in ovarian cancers but have not shown much value in contrast to other malignancies like lung cancer, bladder cancer, etc. Single agent anti PDL1 therapy has shown limited benefit. The combination of nivolumab and ipilimumab has been tried in patients with ROCs with a PFI <12 months, who have received one to three prior lines of therapy. The combination showed superior response rates and longer PFS.[65] Similarly, a combination of pembrolizumab with bevacizumab and metronomic cyclophosphamide in ROC has been studied in a phase 2 trial. It demonstrated a meaningful clinical response in 95% patients and durable responses in 25% of patients.[66] A phase 3 trial of atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in ROCs is under way, the results of which may throw more light on the role of these agents.[67]

Newer avenues like cancer vaccines, adoptive cell therapy, dendritic cell therapy, and oncolytic virus therapy are also being tried in ROC to improve survival especially in the platinum-resistant setting.[68]

Homologous Recombinant DNA (HRD) Testing in ROCs

HRD is tested using three main strategies[69]:

- Germline mutation screening—Germline mutation screening can be performed using next generation sequencing analysis of DNA from blood.
- Somatic mutation screening—Somatic mutation screening is performed on DNA from tumor samples. This analysis can evaluate any mutation (germline and/or somatic) in HR genes and is thus a broader evaluation. Germline analysis of normal cells is still necessary to determine whether the mutation is germline or somatic. Limitations include the variability of tumor samples available and intratumoral heterogeneity.
- The genomic instability secondary to HRD can be tested to assess the genomic scars based on the loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions. This represents a more functional way and an HRD score can be calculated.

Supportive Care

Patients with ovarian carcinomas have excessive occurrences of malignant bowel obstruction and ascites when compared with patients with other cancer types because of extensive peritoneal disease. They require frequent admissions for the same thus deteriorating the quality of life. The most common surgical approach for relieving large bowel obstruction is a diversion stoma. Venting gastrostomy is usually positioned to prevent the prolonged use of a nasogastric tube for decompression. Good symptomatic control can be achieved for bowel obstruction with medical treatment using a combination of glucocorticoids, opioid analgesics, antiemetics, and antisecretory drugs.[70] Insertion of peritoneal catheters (like PleurX peritoneal catheter drainage) and peritoneovenous shunts (like Leveen shunts) can reduce the admission for paracentesis and its complications.[71]

Metronomic Therapy in Ovarian Cancer

Metronomic therapy is described as the chronic administration of low, equally spaced, doses of chemotherapeutic drugs with therapeutic efficacy and low toxicity.

It has proved to modulate the host immune response and tilt the balance from immunosuppression to immunostimulation by several mechanisms. It also has an anti VEGF activity which results in an antiangiogenic effect. Basically, it acts by modulation of the tumor microenvironment.[72]

Various agents that have been used in ROCs include low dose oral cyclophosphamide and etoposide in combination with hormonal agents that have been elucidated earlier.[73] Some single and series case reports have also described the benefit of adding bevacizumab to metronomic therapy with cyclophosphamide.[74] Recently an article showed that a combination of pazopanib plus oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in patients with platinum-resistant or -refractory EOC.[75] This form of therapy is especially important in a resource-constrained setting.

Evaluation of Patients with ROCs

According to GCIG criteria, recurrence based on serum CA 125 levels is defined as a serial elevation of serum CA 125. An imaging with Contrast enhanced Computed Tomography scans is essential for accurate staging of a recurrent disease. This can help in guiding treatment of the disease. Positron emission tomography (PET)-CT scans may reveal sites of disease not visible on CT scans. This becomes a valuable tool to select patients for secondary debulking surgery, by excluding additional sites of disease not seen on CT scans and not amenable to cytoreduction.[76] Diagnostic laparoscopy is only indicated when a secondary cytoreduction is planned to prevent futile laparotomies.

History of Chemotherapeutic Agents in Ovarian Cancer

Twenty years ago, women with advanced ovarian cancer were treated with the alkylating agents melphalan, cyclophosphamide, chlorambucil, and thiotepa—all as monotherapy.[77] A series of studies performed from the mid-1970s onward established cisplatin as one of the most active agents available for ovarian cancer.[78] The North Thames

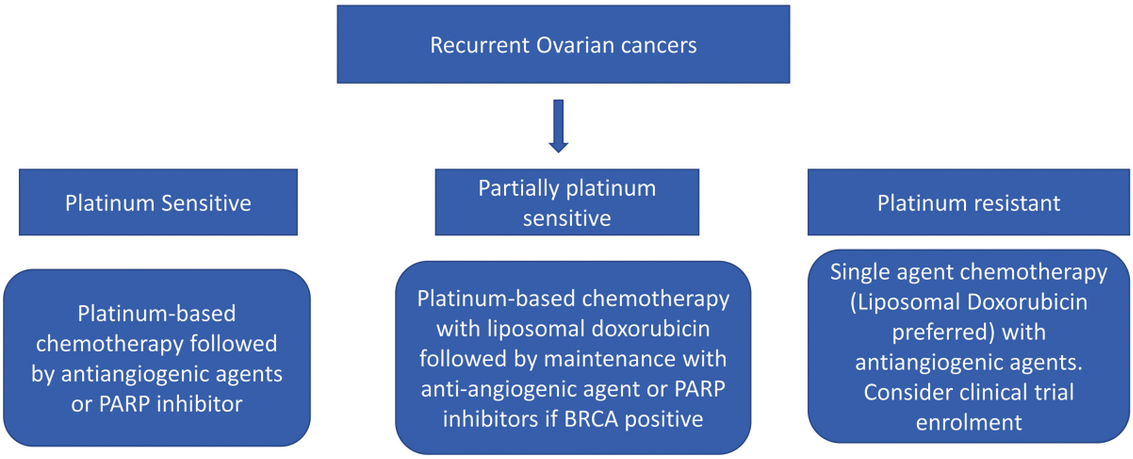

Fig. 2 Treatment algorithm for recurrent high grade serous ovarian carcinomas." There are several mechanisms of cellular resistance to platinum compounds that have been described in various in vivo and in vitro studies. These mechanisms can be classified in two groups.[5,83] NER defects are associated with an exceptional sensitivity to platinum compounds whereas defects of MMR correlate with resistance to the latter.[7,84] NER, nucleotide excision repair.

Cooperative Group reported the results of the first randomized comparison of first-line single-agent cisplatin with an alkylating agent (cyclophosphamide).[79] The possible clinical benefit from the addition of an anthracycline to cisplatin-alkylating agent regimens was studied. A meta-analysis of data from 10 trials showed a modest—but significant—improvement in survival of the triplet regimen.[80] After the discovery of taxanes, the taxane-platinum has become the standard of care. The randomized, controlled trials of first-line cisplatin-based dual therapy showed additional clinical benefit when cyclophosphamide was replaced by paclitaxel.[81,82]

Follow-up of Patients with ROCs

Monitoring is important to detect early signs of a second or subsequent relapse. CA 125 is most common tumor marker which is used for surveillance along with systemic examination. Imaging with ultrasound or CT scan is done only when clinically indicated or when a baseline CA 125 was normal. Most of the guidelines endorses a 3 to 4 monthly follow-up after a recurrence.

Summary

Platinum sensitive ROC (recurrence >12 months)—Rechallenge with platinum in combination with paclitaxel, gemcitabine, or PLD (based on toxicity profile) followed by antiangiogenic agents or PARP inhibitors (especially in BRCA mutant cases).

Partially platinum sensitive ROC (recurrence 6 to 12 months)—Rechallenge with platinum-based chemotherapy in combination with PLD followed by maintenance with antiangiogenic agent. Consider PARP inhibitors if BRCA positive.

Platinum-resistant ROC (recurrence <6 months)—Single agent chemotherapy (PLD preferred) with antiangiogenic agents. Consider clinical trial enrolment.

The schema of the above has been depicted as a flowchart in ►**Fig. 2**.

Conclusion

The landscape of treatment for ROCs has shown extensive advances and refinements. Several molecular targeted therapies like anti-angiogenic agents and PARPi have shown activity in ROCs in addition to conventional chemotherapy. The utilization of these agents has gone a long way in improving survival in these sets of patients. Further progress is warranted especially in platinum-resistant ROC. Identification of newer targets and biomarkers is a paradigm for optimizing the care of this category of patients.

Conflict of Interest
None declared.

Acknowledgment
None declared.

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"A.B.C." of Immunotherapy in Hematological Malignancies...Promise and Perils

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Ind J Med Paediatr Oncol 2024;45:106–114.

Abstract

The treatment landscape of hematological malignancies has been evolving at an extremely fast pace. Hematological malignancies are diverse and distinct from solid tumors. These constitute challenges, which are also unique opportunities for immunotherapy. The five categories of immunotherapies that have found success in the management of hematological malignancies are allogeneic hematopoietic stem cell transplant, monoclonal antibodies and innovative designs, immune checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, and B cell targeting small immunomodulatory molecules. Allogeneic stem cell transplant rightly called our bluntest weapon is the oldest form of successful immunotherapy. Alternate donor transplants and improvement in supportive care have improved the scope of this immunotherapy option. Among monoclonal antibodies, rituximab forms the prototype on which over a dozen other antibodies have been developed. The bispecific T-cell engager (BiTE) blinatumomab engages cytotoxic CD3 T cells with CD19 acute lymphoblastic leukemia (ALL) cells, which is an effective treatment method for relapsed refractory ALL. Immune checkpoint inhibitors have established their role in hematological malignancies with high PD-L1 expression, including relapsed refractory Hodgkin's lymphoma and primary mediastinal B cell lymphoma (BCL). Small immunomodulatory drugs targeting the B cell receptor downstream signaling through BTK inhibitors, SYK inhibitors, PI3K inhibitors (idelalisib), and BCL-2 inhibitors (venetoclax), and immunomodulatory imide drugs (lenalidomide) have also emerged as exciting therapeutic avenues in immunotherapy. CAR T cells are one of the most exciting and promising forms of adoptive immunotherapy. CAR T cells are rightly called living drugs or serial killers to keep patients alive. CAR T cells are genetically engineered, autologous T cells that combine the cytotoxicity of T cells with the antigen-binding specificity of CARs. CARs are antigen-specific but major histocompatibility complex/human leukocyte antigen-independent. There are five approved CAR T cell products for the management of relapsed refractory leukemias, lymphoma, and multiple myeloma. The past and present of immunotherapy have been really exciting and the future looks incredibly promising. The challenges include widening the availability and affordability beyond specialized centers, identification of potentially predictive biomarkers of response, and

Keywords
- allogeneic stem cell transplant
- CAR T cells
- hematological malignancies
- immune checkpoint inhibitors
- immunotherapy
- monoclonal antibodies

article published online
November 28, 2022

DOI https://doi.org/10.1055/s-0042-1749321.
ISSN 0971-5851.

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

experience in the management of complications of these novel agents. The combinational approach of multiple immunotherapies might be the way forward to complement the treatment strategies to harness the immune system and to improve survival with good quality of life.

Introduction

The treatment landscape of hematological malignancies has been evolving at an extremely fast pace. Immunotherapy, the fifth pillar of oncology, is carving a niche for itself in the crowded therapeutic landscape. Harnessing the power of the immune system to fight malignancy has been a dream in oncology. In the recent years, a better understanding of the interaction between the immune system and cancer cells has created novel and powerful forms of immunotherapy. Hematological malignancies are diverse and distinct from solid tumors in many aspects. These constitute challenges that are also unique opportunities for immunotherapy.

In this review, we discuss the past, present, and future of immunotherapy in hematological malignancies and its promise and perils.

Why do Hematological Malignancies Pose Challenges which are also Unique Opportunities for Immunotherapy?

1. All hematological malignancies originate from corrupt immune cells, which are in constant contact with healthy immune cells in the same microenvironment. This makes it conducive to constant immune surveillance.
2. All hematological malignancies are diseases of primary and secondary lymphoid organs. Normal immune cell development and differentiation also happens in the same sites. Hence, malignant cells can hijack the niche that belongs to normal immune cells.
3. Acute leukemia arises from hematopoietic stem cells, leading to deficient hematopoiesis, cytopenia, and immunosuppression.
4. Many hematological malignancies have a low tumor mutational burden.
5. Blood is easily accessible to sample immune cells for modification, cell engineering, and reinfusion.
6. Many hematological malignancies have precursor states which can help in studying the role of immune surveillance.

What are the Immunotherapy Options that have Found Success in Hematological Malignancies?

There are five categories of immunotherapies (A.A.B.B.C.C.) that have found success in the management of hematological malignancies, which will be discussed in this review.

[Acronym of A.A.B.B.C.C.]

1. **A**llogeneic hematopoietic stem cell transplant.
2. Monoclonal **A**ntibodies and innovative designs of ADC and **B**iTES (bispecific T-cell engager).
3. **B** cells as ripe targets: small immunomodulatory molecules.
4. Immune **C**heckpoint inhibitors.
5. **C**AR T cells (►**Fig. 1**).

1. Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (AlloHSCT) is the earliest form of successful cancer immunotherapy in hematological malignancies. The first AlloHSCT was performed by Dr. Donnall Thomas in 1968. This still holds today as one of the most curative treatment modalities in hematological malignancies. It is often called the chemotherapist's bluntest weapon, as it does carpet bombing eradicating both the hematopoietic and immune systems

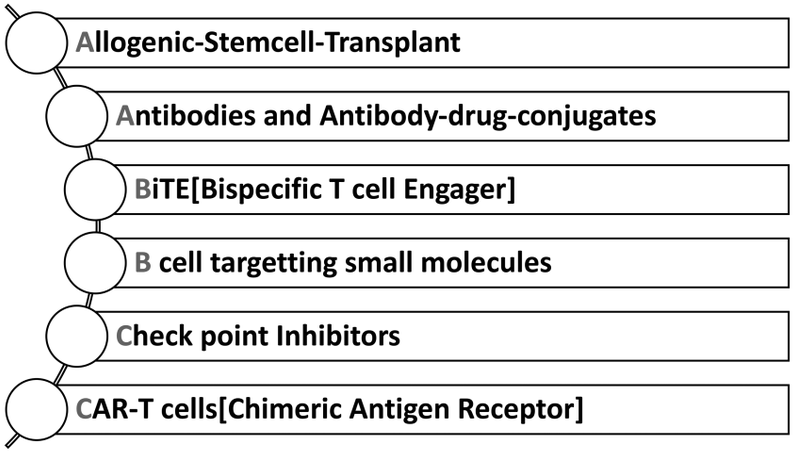

Fig. 1 The "A.B.C." of immunotherapies in hematological malignancies.

of the patient. This forms an ideal model to take our knowledge forward on immunotherapy.

The proof of principle of sensitivity of graft-versus-leukemia (tumor) effect[1,2] comes from the efficacy of AlloHSCT in refractory disease settings,[3,4] the success of donor lymphocyte infusion/withdrawal of immunosuppression in relapsed setting,[5] and the use of conditioning regimens (reduced intensity/non-myeloablative] that depend[6] more on the immunological rationale and less on chemotherapy dose for disease eradication.

The increasing use of alternate donor transplants and improvements in nonrelapse mortality with advanced supportive care is improving the outcomes. Haploidentical donor transplant with posttransplant cyclophosphamide has outcomes comparable to matched unrelated donor transplants.[7,8] These novel strategies have revolutionized the field of allogeneic stem cell transplant.

2. Monoclonal Antibodies and Innovative Designs

Passive immunotherapy with monoclonal antibodies is one of the most commonly used forms of immunotherapies in hematological malignancies. Rituximab, the first Food and Drug Administration (FDA)-approved monoclonal antibody in oncology, is a type 1 anti-CD20 antibody used to treat B cell malignancies. Since then, it has become the prototype for the development of other monoclonal antibodies.

Monoclonal antibodies[9] are developed based on either lineage-specific antigens (LSAs) or non-LSAs (NLSAs).

- LSAs are antigens specific to different stages of the same lineage of hematopoietic differentiation like CD20 for B cells and CD3 for T cells.
- NLSAs are antigens that play important roles in the malignant transformation of cells and are not restricted to a specific hematopoietic lineage of cells. These can be oncogenic receptors or glycoproteins like CD52 for chronic lymphocytic leukemia and SLAMF7 for multiple myeloma.

Mechanisms of action:

- Antibody-dependent cellular cytotoxicity.
- Antibody-dependent phagocytosis.
- Complement-dependent cytotoxicity.
- Direct cytotoxicity and apoptosis.

3. Bispecific T Cell Engagers and Bispecific Killer Cell Engagers

Bispecific antibodies are an innovative design in which single-chain variable fragments of two antibodies are fused to give specificity for two different antigens.

- BiTE is a type of bispecific antibody, in which one target is T cell engaging domain with anti-CD3 antibody and the other target is tumor-associated antigen such as anti-CD19 antibody in acute lymphoblastic leukemia (ALL). The binding of BiTE to two targets mediates a cytolytic synapse resembling a natural immunological synapse. Blinatumomab, a CD3 × CD19 BiTE, is the only FDA-approved BiTE for the treatment of R/R B cell precursor ALL (pre–B-ALL).[10–12] Blinatumomab in relapsed refractory B-ALL with active disease yielded a complete response (CR) rate of 43%, while patients with minimal residual disease had a CR rate of 80%. Blinatumomab-based combination immunotherapy is being tested.
- Bispecific killer cell engagers are bispecific antibodies targeting natural killer cell receptor CD16. They are in the process of development with the hope of utilizing the power of the innate immune system.

►**Table 1** gives a comprehensive list of approved monoclonal antibodies used in the treatment of hematological malignancies.

4. Immune Checkpoint Inhibitors: Checkmate with Checkpoint Inhibitors

The introduction of immune checkpoint inhibitors (ICIs) as immunomodulatory antibodies, has gained spotlight in the management of several solid malignancies like melanoma, non–small cell lung cancer, renal cell carcinoma, and urothelial bladder cancers. The primary targets for checkpoint inhibition have been programmed cell death receptor-1 (PD-1) or programmed cell death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). They are negative regulators or brakes of the immune system that help the cancer cells evade immune surveillance. Their established role in hematological malignancies is currently limited to tumors with high PD-L1 expression, including Hodgkin's lymphoma (HL) and primary mediastinal B cell lymphoma (PMBCL).

4.1 Why the Success of ICI in Hodgkin's Lymphoma?

The therapeutic benefit of PD-1 blockade is best demonstrated in patients with HL.

The unique immunological milieu of HL that could critically contribute to the success of ICI therapy include:

1. The immunologically hot (or inflamed) tumor microenvironment (TME) of classical HL (cHL) consists of malignant Hodgkin Reed-Sternberg cells (less than 1%) and an abundant inflammatory immune cell infiltrate which is different from the TME observed in non-HL (NHL).[13,14]
2. Amplification of 9p24.1 (locus-containing JAK2/PDL1/PDL2), induces aberrant overexpression of PD-L1 on malignant cells.[15]
3. Epstein–Barr virus (EBV) infection contributes to PD-L1 upregulation.[16] EBV-positive Hodgkin cases have been shown to have higher PD-L1 expression levels.[17]

4.2 Evidence for ICI in Hodgkin's Lymphoma and PMBCL

The early studies in heavily pretreated Hodgkin's patients, receiving either nivolumab[18] or pembrolizumab[19] were very encouraging. This led to larger phase 2 trials (CHECKMATE 205[20–22] and KEYNOTE-087,[23] respectively). These two studies had several similarities, with some significant differences resulting in variance in approved indications during licensing. Both studies included three cohorts of patients defined according to prior autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) exposure (►**Table 2**), but only KEYNOTE-087[23] included patients who were transplant-naive (a cohort of patients deemed transplant-ineligible, mainly because of chemo-refractoriness). The overall response rates were similar

Table 1 The monoclonal antibodies approved for the treatment of hematological malignancies

Name	Target	Indications	Approval year	MOA	Reference
Rituximab	CD20	B-NHL, DLBCL, CLL, FL	1997, 2006, 2010, 2011	CDC, ADCC, PCD	25–28
Ofatumumab	CD20	CLL	2009	CDC, ADCC, PCD	29
Obinutuzumab	CD20	CLL, FL	2013, 2016	CDC, ADCC, PCD	30,31
Tafasitamab	CD19	DLBCL	2020	ADCC/ADCP	32
Alemtuzumab	CD52	CLL	2001	ADCC/CDC/ADCP	33,34
Mogamulizumab	CCR4	MF, SS	2018	ADCC	35
Daratumumab	CD38	MM	2016	ADCC/CDC/ADCP	36
Isatuximab	CD38	MM	2020	ADCC/CDC/ADCP	37
Elotuzumab	SLAMF7	MM	2015	ADCC	38
Brentuximab	CD30	HL, ALCL	2011, 2018	ADC	39,40
Moxetumomab	CD22	HCL	2018	ADC	41
Gemtuzumab	CD33	AML	2017, 2020	ADC	42,43
Polatuzumab	CD79b	DLBCL	2019	ADC	44

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; B-NHL, B non-Hodgkin's lymphoma; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; HL, Hodgkin's lymphoma; MF, mycosis fungoides; MM, multiple myeloma; MOA, monoclonal antibody; PCD, programmed cell death; SS, Sézary syndrome.

in both studies at approximately 70%, with most being partial. CRs were documented in 14 to 32%, depending on the study cohort. The median duration of response ranged from 11 to 25 months. The overall survival rate at 2 years exceeded 85% in all cohorts. These impressive results led to regulatory approvals for patients who had failed ASCT and brentuximab (BV) for both drugs, with additional approval for pembrolizumab in the setting of ASCT ineligibility and failure of BV.

PMBCL shares many histologic and genetic features with HL, including aberrations at 9p24 and overexpression of PD-L1. Objective response rates of approximately 46% were reported in the phase IB KEYNOTE-013 ($n = 21$) and phase II KEYNOTE-170 ($n = 53$) pembrolizumab studies, with a CR rate of 13% in the larger phase II study. Progression-free survival was significantly associated with PD-L1 expression, which in turn was associated with the magnitude of the 9p24 abnormality. As with HL, combination strategies with anti-PD-1 antibodies are also being evaluated.

Unlike cHL and PMBCL, PD-L1 overexpression is not commonly seen on B NHL cells. There is some evidence of 9p24 mutations in primary testicular lymphoma and primary central nervous system diffuse large B cell lymphoma, with selected use in these specific subgroups.

4.3 Approved Indications for Immune Checkpoint inhibitors in Hematological Malignancies

Nivolumab

1. Relapsed and refractory HL post-autologous HSCT (auto-HSCT) and brentuximab.
2. Relapsed HL after three or more lines of therapy including auto-HSCT.

Pembrolizumab

1. Relapsed and refractory HL in adults post-auto-HSCT and brentuximab.
2. Pediatric relapsed/refractory HL.
3. Relapsed HL post two or more lines of therapy.
4. PMBCL: adult and pediatric patients with refractory PMBCL, or who have relapsed after two or more prior lines of therapy. (Limitations of Use: it is not recommended for the treatment of PMBCL patients who require urgent cytoreductive therapy.)

4.4 The Challenges in Immune Checkpoint Inhibitors Therapy and Potential Solutions to Overcome Them

1. Antigen presentation: The use of major histocompatibility complex (MHC)-independent treatment options like chimeric antigen receptor T cell therapy (CAR T cell therapy) or BiTE.
2. Tumor-associated macrophages resistance: Anti-cerebrospinal fluid antibodies or phosphatidyl 3-kinase-γ (PI3K) inhibitors.
3. TME: Novel checkpoint inhibitors like LAG-3 (lymphocyte activation gene-3) and TIM-3 (T cell immunoglobulin and mucin-domain containing-3) inhibitors.
4. Genetic and epigenetic factors: Epigenetic therapies like deoxyribonucleic acid methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi).
5. Immunosuppressive metabolites: Indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor like epacadostat.
6. Biomarker response: Identify biomarkers beyond PD-1/PDL-1/TMB like serum interferon-γ levels and CD8-positive tumor-infiltrating lymphocytes.

Table 2 Landmark trials of immune checkpoint inhibitors in Hodgkin's lymphoma

	CHECKMATE-205 (nivolumab)			KEYNOTE- 087 (pembrolizumab)		
	Arm A	Arm B	Arm C	Cohort 1	Cohort 2	Cohort 3
Patient features	Failed ASCT, brentuximab-naive	Failed ASCT and brentuximab	Failed ASCT, brentuximab exposed before/ after ASCT	Failed ASCT and brentuximab	ASCT ineligible, failed chemo and brentuximab	Failed ASCT, no subsequent brentuximab
Number of patients	63	80	100	69	81	60
Median age (y)	33	37	32	34	40	32
Prior lines of treatment	2	4	4	4	4	3
ORR (%)	65	71	75	77	67	73
CR rate (%)	32	14	20	26	26	32
PFS (mo)	17	12	15	16	11	19
OS at 2 y (%)	90	86	86	93	91	89

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; ORR, objective response rate; PFS, progression-free survival.

►**Table 2** shows the results of landmark immunotherapy trials that led to the approval of ICI in HL.

5. B Cells Ripe Target Small Molecules

Small immunomodulatory drugs targeting the B cell receptor downstream signaling through BTK inhibitors, SYK inhibitors, PI3K inhibitors, and BCL-2 inhibitors, and immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide) have also emerged as exciting therapeutic avenues in immunotherapy.

6. CART Cells AS “Living Drugs” OR “Serial Killers” to Keep Patients Alive

CAR T cells are one of the most exciting and promising forms of adoptive immunotherapy. CAR T cells are rightly called living drugs or serial killers to keep patients alive. CAR T cells are genetically engineered, autologous T cells that combine the cytotoxicity of T cells with the antigen-binding specificity of CARs. CARs are antigen-specific but MHC/human leukocyte antigen-independent.

6.1 CAR Design and Generations: CARs in Nut and Bolt Phase...

CARs are artificial transmembrane proteins. They have three domains[24]:

(a) *Extracellular ectodomain* with two parts:
1. Antigen-binding domain: confers specificity to the product. It is usually a single-chain variable fragment of an antibody that recognizes and binds to specific tumor-associated antigens on cell surfaces like CD19 on the surface of B cells.
2. Spacer: is a flexible hinge that decides the orientation of the ectodomain and keeps it away from the cell surface to bind effectively with the antigens.

(b) *Transmembrane domain*: is to effectively anchor the CAR on the T cell membrane.

(c) *Intracellular endodomain*:

This is the signaling domain which consists of the CD3ζ chain and costimulatory signaling domains (CD28/41BB) and cytokines. This decides the construct of successive generations of CARs with improved cytotoxicity, proliferation, engraftment, and persistence.

Generation 1 CAR: Signaling domain with only CD3 chain.

Generation 2 CAR: Signaling domain with CD3 and one other costimulatory domain like CD28.

Generation 3 CAR: Signaling domain with CD3 and two other costimulatory domains.

Generation 4 CAR or TRUCK (“T cells redirected for antigen-unrestricted cytokine-initiated killing”): Combines the direct cytotoxicity of CAR T cell with immune modulation of cytokines.

6.2 CAR T Cells on a Test Drive to the Clinic: Cell-Processing Procedure and Steps

1. Harvesting of autologous T cells by leukapheresis.

2. Stimulation with T cell mitogen (magnetic microbeads coated with mitogenic antibody).
3. Transduction of CARs into T cells with a viral vector.
4. Expansion and culture of T cells.
5. Cryopreservation of CAR T cell product.
6. Lymphodepleting conditioning to patient.
7. Thawing and reinfusion of CAR T cell product to the patient.
8. Monitoring and follow-up.

6.3 Causes of Chimeric Antigen Receptor T Cell Treatment Failure

Failure to Receive the CAR T Cell Product on Time
A significant proportion of patients might fail to receive the CAR T cell product on time due to rapidly progressive disease in the relapsed refractory state, long manufacturing times, and failed manufacture. Possible solutions include shifting CAR T cells earlier in the treatment landscape, improvement in the manufacturing process with shorter times of release of the product, and finally off the shelf allogeneic CAR T cells.

Antigen-Negative Escape
Relapse with antigen-negative disease is the most important reason for treatment failure. This can be targeted with bispecific or trispecific CAR T cells.

Failure of Chimeric Antigen Receptor T Cell Engraftment or Expansion
CD19+ relapse of B-ALL after initial remission occurs due to loss of T cell persistence/engraftment. It is usually due to patient-related factors like age, disease burden, and comorbidities, CAR-related factors like CAR construct with costimulatory molecules, murine ectodomain, and viral vector used for transduction, and fitness of T cell. This could be improved by modified CAR constructs like humanized proteins.

6.4 Toxicity Caused by Chimeric Antigen Receptor T Cells

- Cytokine release syndrome.
- Neurotoxicity or "immune cell-associated neurotoxicity syndrome" (ICANS).
- Off-tumor, on-target toxicity: B cell aplasia and hypogammaglobulinemia.
- Post–CAR cytopenia.

6.5 Future Directions for Chimeric Antigen Receptor T Cell Therapy

- Strategies to improve efficacy: Dual antigen targeting with dual signaling/bispecific tandem CAR.
- Strategies to improve specificity: Switchable suicide gene switch CAR and synthetic splitting receptor CAR.
- Strategies to reduce immunotoxicity: Detuning and tuning of CAR T cells.
- Dasatinib to induce reversible inactivation.
- Addressing antigenicity with humanized CARs.
- Universal CARs.
- "Off-The-Shelf" allogeneic CAR T cells.
- TRUCKS.
- Combinational strategies with immune checkpoint inhibitors/AlloHSCT/BiTES.

A summary of the approved CAR T cell products and their landmark trials is given in ►**Table 3**.

The summary of immunotherapy options in hematological malignancies is depicted in ►**Fig. 2**.

Limitations of this Review

- There is no detailed probing of clinical trials or weighing of evidence that led to the approval of various immunotherapy options.
- There is no elaboration on the side effect profile and management strategies of immunotherapy complications.

Questions and Future Directions in Immunotherapy

- How to widen the availability of immunotherapy options?
- How to screen for potential prognostic and predictive biomarkers of response?
- What is the best combination treatment strategy and rational sequence?
- How to effectively reduce the off-target and on-target toxicities?
- What is the role of gut-microbiome in immune responses?
- What would be the best surrogate endpoints in clinical trials of immunotherapy?
- How is the quality of life of patients affected by immunotherapy?
- How can we make these magic bullets more affordable to our patients?

Conclusion

The past and present of immunotherapy have been really exciting and the future looks incredibly promising. The challenges include widening the availability and affordability beyond specialized centers, experience in the management of complications of these novel agents, and defining appropriate endpoints for response assessment of these agents. The combinational approach of multiple immunotherapies might be the way forward, to complement the treatment strategies, harness the immune system, and improve quantity and quality of life. Hopefully, in the future, we can dream of a synergism of the vision of Dr. Donnall Thomas and Paul Ehrlich, where "the bluntest weapon" may be combined with novel immunotherapies as "true magic bullets."

Conflict of Interest
None declared.

Table 3 Approved CAR T cell products and landmark trials

CAR T cell product name	Indication	Year of approval	Trial name	Results	Ref:-
Tisagenlecleucel	Relapsed refractory ALL	2017	ELIANA	CR: 81%, EFS: 50%, OS: 76%	45
Axicabtagene	Relapsed refractory DLBCL, PMBCL	2017	ZUMA-1	ORR: 82%, CR: 58%, PFS: 44%	46
Tisagenlecleucel	Adult R/R DLBCL	2018	JULIET	ORR: 52%, CR: 40%, OS: 49%	47
Brexucabtagene	Mantle cell lymphoma	2020	ZUMA-2	ORR: 93%, CR: 67%, PFS: 61%, OS: 83%	48
Lisocabtagene	R/R large B cell lymphoma	2021	TRANSCEND	ORR: 75%, CR: 53%, PFS: 44%, OS: 58%	49
Axicabtagene	R/R follicular lymphoma	2021	ZUMA-5	ORR: 94%, CR: 80%, PFS: 74%, OS: 93%	50
Idecabtagene	Multiple myeloma	2021	KarMMa	ORR: 73%, CR: 33%, PFS: 8.8 months, OS: 78%	

Abbreviations: ALL, acute lymphoblastic leukemia; CAR T cell, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B cell lymphoma.

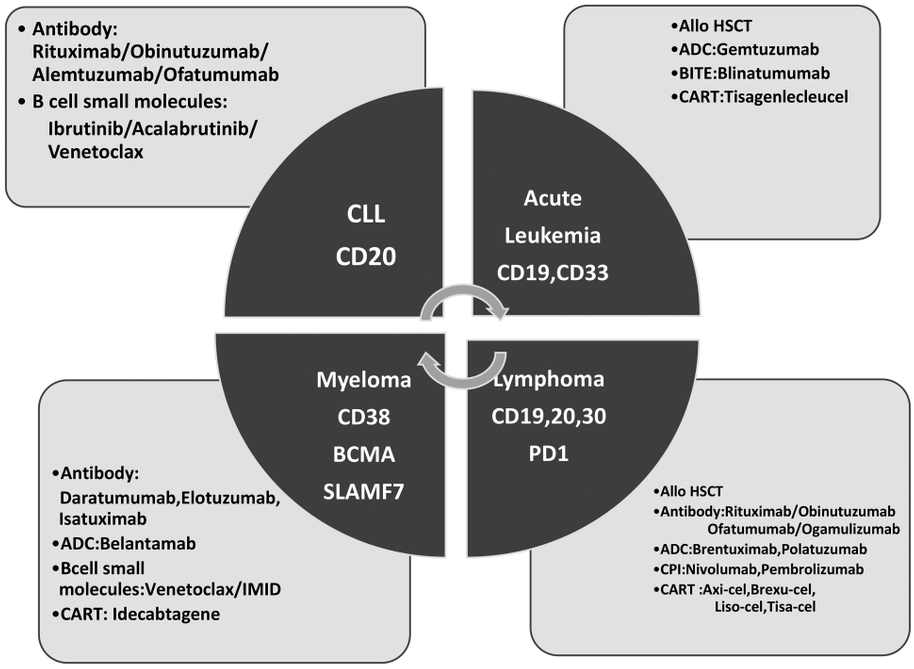

Fig. 2 Summary of immunotherapy in hematological malignancies.

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FLT3 and IDH1/2 Inhibitors for Acute Myeloid Leukemia: Focused Clinical Narrative Review of Forthcoming Drugs from an Indian Context

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Ind J Med Paediatr Oncol 2024;45:115–126.

Abstract

Therapeutic approaches for acute myeloid leukemia (AML) have witnessed minimal evolution in recent decades, primarily relying on advancements in supportive care and transplantation to drive improvements in overall survival rates. However, treatment with intensive chemotherapy may not be feasible for patients with advanced age or reduced fitness, and outcomes for patients with relapsed/refractory disease continue to be suboptimal. Several agents with a novel mechanism of action have been developed in the past decade and have shown efficacy in patients with both newly diagnosed and relapsed AML. Out of these, several FLT3 (FMS like tyrosine kinase 3) and IDH1/2 (isocitrate dehydrogenase 1/2) inhibitors have received regulatory approval in specific clinical settings and are available for clinical use. This is an actively expanding field with several ongoing clinical trials in advanced phases. We provide a focused narrative review of drugs from these two categories with available clinical data.

Keywords
- myeloid
- leukemia
- FLT3
- midostaurin
- gilteritinib
- sorafenib

Introduction

Drug therapy for acute myeloid leukemia (AML) has remained largely unchanged since the introduction of the "7 + 3" regimen in 1973, with most of the subsequent improvement in survival attributable to advances in supportive care, infection control, and allogeneic stem cell transplantation.[1,2] Risk-adapted use of intensive chemotherapy and stem cell transplantation following induction now allows 30 to 50% of younger, medically fit patients to achieve long-term cure.[3,4] Despite these advances, reliance on intensive chemotherapy presents several challenges that prevent optimal outcomes in specific clinical settings. First, intensive chemotherapy is often precluded by advanced age, reduced patient fitness, and/or financial limitations. A significant proportion of patients older than 60 years of age may not be candidates for intensive therapy and receive hypomethylating agents alone.[5] Improvements in survival over the past few decades have eluded older patients with AML, even in developed nations and necessitate newer nonchemotherapy approaches.[6] Second, relapsed or refractory disease is still associated with a poor long-term survival worldwide and is expected to benefit from newer therapies, similar to other hematologic malignancies.[7]

Several of these challenges are addressed by targeted oral agents, which represent the first drug approvals for AML in the past few decades. These small molecule inhibitors have demonstrated efficacy in both newly diagnosed and relapsed settings and are gradually transitioning to first-line therapy in combination or even as monotherapy, offering a new treatment approach for unfit patients who would not receive any treatment in the past.[4,8] These advances are relevant for India, where despite a lower age of presentation, physiological frailty is evident and very few patients over the age of 60 years

article published online
February 9, 2024

DOI https://doi.org/10.1055/s-0044-1779621.
ISSN 0971-5851.

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

receive intensive chemotherapy with curative intent.[5] Further, survival after relapsed disease in India is suboptimal, with low rates of allogeneic stem cell transplantation, warranting the introduction of newer, less toxic treatment options.[9]

Oral agents for AML are categorized based on their distinct cellular targets, each exhibiting unique mechanisms for efficacy and toxicity. We present a succinct and targeted review that incorporates the available supporting evidence and clinical application of presently accessible targeted oral agents (FMS like tyrosine kinase 3 [FLT3] inhibitors and isocitrate dehydrogenase 1/2 [IDH1/2] inhibitors) for AML.

Isocitrate Dehydrogenase Inhibitors

Cellular Mechanism

IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate (α-KG) by oxidative decarboxylation along with simultaneous reduction of NADP to NADPH. IDH1 and IDH2 are isozymes with significant sequence similarity and are mutated in several malignancies.[10] IDH3 is structurally distinct and does not have a defined pathogenic role at present. Relevant mutations in *IDH1* and *IDH2* were first identified in 2011, and since then have been consistently demonstrated at a frequency of 10 to 20% in patients with AML.[11,12] Mutations in *IDH1/2* modify the metabolic pathway to produce R-2- hydroxyglutarate instead of α-KG, leading to inhibition of several α-KG-dependent enzymes. This leads to a cellular differentiation block by inhibiting several enzymes involved in histone and DNA methylation.[13] Downstream effects from altered cell differentiation and cell cycle control promote leukemogenesis in vitro and are viable targets for inhibition in patients with AML.[14] Both IDH1 and IDH2 mutations have a similar mechanism of contributing to pathogenesis of AML. T Common point mutations noted in IDH1 and IDH2 are R132H and R172K, respectively, and are mutually exclusive.

Enasidenib

IDH2 mutations are noted in approximately 10 to 12% of patients with AML and frequently occur along with mutations in genes affecting epigenetic pathways (*ASXL1*, *SRSF2*, *RUNX1*, and *STAG2*).[15] Enasidenib is a selective *IDH2* inhibitor that was first shown to be effective in mouse xenograft models, significantly reducing cellular 2-KG levels, promoting cellular differentiation and improving survival.[16] Its safety and clinical activity as monotherapy was documented in a phase 1b dose escalation study, which included 239 patients with relapsed AML. An overall response rate (ORR) of 40.4% and a complete remission (CR) rate of approximately 19.3% was observed, with a median time to CR of 3.8 months (range, 0.5–11.2). Median overall survival (OS) was 9.3 months, with survival at 1 year of approximately 39%.[17] The most significant nonhematologic toxicity was differentiation syndrome (DS), observed in approximately 8% of patients. Further analysis of these data indicated that DS was more likely in patients with higher bone marrow blast counts and typically observed after a median of 30 days (range, 7–129) from starting treatment. Importantly, DS was reversed with temporary cessation of enasidenib and early initiation of steroids in all patients.[18]

Enasidenib exhibited effectiveness as a standalone treatment as well in 37 patients in the above cohort with previously untreated IDH2-mutated AML who were not eligible for standard therapy. In this cohort with a median age of 77 years, an ORR of 37.8% and CR of 19% was observed. Median OS was 10.4 months, indicating potential efficacy as first-line monotherapy.[19]

A recent phase 3 trial (IDHentify) evaluated patients older than 60 years of age with relapsed or refractory disease after failure of at least two lines of therapy. A total of 267 patients underwent randomization, with equal distribution between the enasidenib group and the conventional low-dose therapy group. Although no statistically significant disparities in OS were identified (6.8 vs. 6.2 months), the enasidenib cohort exhibited higher rates of complete response (26 vs. 3%) and ORR (41 vs. 11%).[20] A recent update of these data presented in the 2022 American Society of Clinical Oncology (ASCO) meeting showed a specific OS advantage for patients with the R172 mutation (14.6 vs. 7.8 months), which was not seen with patients with R140 mutations.[21]

Based on efficacy in patients with newly diagnosed AML, enasidenib was evaluated in a pragmatic combination with azacytidine in a phase II trial including patients with IDH2-mutated AML. A total of 26 patients were included (19 relapsed and 7 newly diagnosed) to receive enasidenib and azacytidine, with concomitant FT3 inhibitors and venetoclax allowed. Cumulative CR was noted in 100% of newly diagnosed patients and 58% with relapsed/refractory disease. This combination was well tolerated with a 6-month OS of 70% in newly diagnosed patients with median OS not reached after 11 months of follow-up period.[22] Comparable outcomes were achieved in a multicenter phase 2 trial that randomized participants to receive either azacytidine alone or in combination with enasidenib. The combined therapy demonstrated a notably superior ORR of 74% compared with 36% in the azacytidine monotherapy group.[23]

Of significant clinical interest, enasidenib was found to be safe in combination with venetoclax for pretreated patients with IDH2-mutated AML, showing an ORR of 55%.[24] Further dose finding studies of this combination are ongoing.

Ivosidenib

Ivosidenib (AG-120) was the first in-class IDH1 inhibitor developed with activity against several solid tumors.[25] It's clinical activity in AML as monotherapy was documented in a phase 1 study including 258 patients with relapsed/refractory disease following a median of two prior lines of therapy.[26] The rate of CR + CR with incomplete count recovery (CRi) was 30%, with median time to CR of 2.7 months and median OS of 14.5 months. It was well tolerated with the most common nonhematologic toxicities being QTc prolongation (7.8%) and DS (3.9%). Based on these data, it received U.S. Food and Drug Administration (FDA) approval in 2018 for patients with relapsed/refractory *IDH1*-mutated AML.

Ivosidenib also demonstrated single-agent activity in newly diagnosed patients ineligible for standard

chemotherapy (median age, 76 years), with CR + CRi rates of 42.4% and a median OS of 12.6 months.[27] It's safety and activity in combination with azacytidine in a phase 1b trial in patients with IDH1-mutated AML formed the basis for the randomized phase 3 AGILE trial, which led to regulatory approval for newly diagnosed patients in this setting.[28,29] This trial included 146 newly diagnosed patients who were randomized to azacytidine alone or in combination with ivosidenib. Combination therapy was associated with a higher median OS (24 vs. 7.9 months) and lower risk of treatment failure, relapse, or death (hazard ratio [HR] = 0.33, 95% confidence interval [CI] = 0.16–0.69) compared with azacytidine alone. Unique nonhematologic adverse effects in the ivosidenib arm included QT prolongation in 20% and DS in 14% patients. Following the evidence from these findings, the FDA granted approval to ivosidenib in May 2022 for its utilization in combination with azacytidine as a treatment option for newly diagnosed patients with IDH1-mutated AML.

Ivosidenib and enasidenib are also being evaluated in combination with intensive cytotoxic chemotherapy in newly diagnosed patients with *IDH1/2*-mutated AML. In 2021, the publication of phase 1 data presented findings from a study involving a cohort of 60 patients who received ivosidenib and 91 patients who received enasidenib in combination with intensive chemotherapy.[30] This study observed CR in 55 and 47% and CRi in 72 and 63% patients with ivosidenib and enasidenib, respectively. The median OS in the ivosidenib cohort was not reached and with enasidenib was 25 months. Among patients achieving CRi, minimal residual disease (MRD) negativity was noted in 80 and 63%, respectively. This study indicated the feasibility of adding IDH1/2 inhibitors along with intensive chemotherapy for newly diagnosed patients.

Ivosidenib is metabolized by the CYP3A4 enzymes, and drug toxicity can potentially increase in the presence of strong CYP3A4 inhibitors such as posaconazole and voriconazole. The manufacturer recommends reducing the dose to 250 mg once a day when used with concomitant azoles due to a higher risk of QTc prolongation.[31] However, a population pharmacokinetic analysis observed that increasing area under the curve (AUC) in the presence of azoles was not associated with an increase in clinical toxicity, likely indicating a wide therapeutic window.[32] As a result, the current expert opinion is to exercise "caution" in the presence of azoles and monitor the QTc interval closely while continuing the drug at the full dose of 500 mg per day.[33]

No significant safety concerns were highlighted on using a combination of ivosidenib with azacytidine and venetoclax in a phase Ib/III study, indicating a potentially new combination for IDH1-mutated AML.[34]

Olutasidenib

Olutasidenib (FT-2102) is a potent, selective IDH1 inhibitor, designed to induce differentiation of cells with mutated IDH1.[35] It was first evaluated in a phase 1 trial including 31 patients with IDH1-mutated AML or MDS, where an ORR of approximately 33% was documented.[36] Dose escalation and safety of combination with azacytidine was subsequently evaluated in a similar patient population, where an ORR of 39% for single agent and 54% for combination therapy was noted. Importantly, 40% patients had mutation clearance, with mIDH1 Variant Allele Frequency (VAF) of <1% after treatment. DS was observed in 13% patients, which was reversible with drug discontinuation.[37]

The phase 1 component of a multicenter trial (NCT NCT02719574) evaluating olutasidenib was published in 2022, including patients with IDH1-mutated AML or MDS both as single agent ($n = 32$) and in combination with azacytidine ($n = 46$) For patients with relapsed AML, ORR of 41% as monotherapy and 46% as combination were observed.[38] For treatment-naïve patients, response rates of 25% for monotherapy and 77% for combination were observed.

The phase II component of the multicenter trial planned to evaluate the efficacy of olutasidenib both as single agent and in combination with azacytidine for patients with AML/MDS. The final analysis included 153 patients with IDH1-mutated AML after a median of two lines of therapy, of which 147 were evaluable. In this subset, monotherapy with 150 mg twice a day was initiated, with ORR of 48% and CR + CRi rates of 35%. The median duration of overall response was 11.7 months and median OS was 11.6 months.[39] Based on this study (2102-HEM-101), olutasidenib received FDA approval in December 2022 as monotherapy for patients with relapsed/refractory AML at a dose of 150 mg twice a day.

Phase 2 data on treatment-naïve patients was presented in 2021, in which patients were divided into four cohorts based on prior therapy and exposure to IDH1 inhibitors or Hypomethylating agents (HMAs).[40] In treatment-naïve patients, ORR of 64% and CR of 45% was documented. In R/R disease without previous HMA or IDH1 inhibitor exposure, similar response rates and median CR duration of 16 months was documented.

FMS-Like Tyrosine Kinase 3 Inhibitors

Cellular Mechanism

FLT3 is a receptor kinase required for hematopoietic cell proliferation and differentiation.[41] The presence of FLT3 mutations was initially discovered in patients with AML in 1996, and since then, it has been recognized as one of the most frequent mutations observed in AML. Approximately 25% of all patients with AML have the FLT3 internal tandem duplication (FLT3-ITD) and 5% have a tyrosine kinase domain (FLT3-TKD) mutation.[42] The pathogenic mechanism of the FLT3-ITD mutation is complex and is described in a succinct review by Friedman et al.[43] FLT3-ITD mutations give rise to the dissociation of the intracellular juxtamembrane domain from the FLT3 receptor, resulting in persistent downstream activation of phosphorylation and subsequent cellular proliferation.

Mutations in FLT3 do not lead to an AML phenotype in isolation, indicating that these mutations are late events with a greater role in altering disease phenotype than disease initiation, in contrast to BCR/ABL1 mutations in chronic myeloid

leukemia.[44] Most initial studies therefore focused on combining FLT3 inhibitors with standard treatment rather than as monotherapy. FLT3 mutations also have a role in posttransplant relapse, providing an impetus for several studies using FLT3 inhibitors in posttransplant maintenance.[45]

First-Generation Inhibitors

Sorafenib, midostaurin, lestaurtinib, and sunitinib are among the first-generation FLT3 inhibitors, characterized by their ability to inhibit multiple kinases. As a result, several off target adverse events are noted with this group of drugs.[46]

Sorafenib

Sorafenib, an orally administered multikinase inhibitor, was developed in 2001 and subsequently gained approval for the treatment of various solid tumors. It was first demonstrated to have activity against AML cell lines in vitro in 2008, indicating potential clinical benefit. Importantly, sorafenib-induced apoptosis in AML was synergistic with cytarabine and BCL2 inhibitors.[47] Clinical activity and safety of sorafenib was demonstrated in a phase I study including 50 unselected patients with advanced MDS or relapsed acute leukemias. A significant reduction in blast count, especially in FLT3-mutated AML was observed with sorafenib monotherapy.[48] As a synergistic action with chemotherapy was known, further clinical studies were largely performed as part of combination therapy.[49]

Sorafenib was shown to be safe and effective in combination with intensive chemotherapy with idarubicin and cytarabine in a phase I/II study including 51 patients. The initial rates of CR were promising, being 75% for the overall cohort and 93% in those with FLT3 mutations.[50] Further follow-up of this study included 62 patients and confirmed a higher rate of initial CR and CR with Partial count recovery (CRp) in patients with FLT3 mutations (95 vs. 83%) but failed to show a durable clinical benefit. Survival was inferior among patients with FLT3 mutations compared with wild type FLT3, with OS of 15.5 vs. 42 months and DFS of 9.9 vs. 17.3 months, primarily owing to high rates of relapse in this subgroup.[51] A similar combination also failed to show any advantage of adding sorafenib to intensive chemotherapy in a randomized trial including 200 newly diagnosed patients unselected for FLT3 mutations.[52]

The SORAML trial, a recent randomized study, featured sorafenib in combination with intensive chemotherapy and enrolled newly diagnosed patients below the age of 60. This phase 2 trial examined the effects of sorafenib in the specified patient population, including 276 patients (chemotherapy + sorafenib 134, chemotherapy + placebo 133). Patients were not selected for FLT3 mutations, which were present in 17% of patients in both arms. There was no significant difference in rates of CR among both arms (60 vs. 59%). After a median follow-up of 36 months, median event-free survival (EFS) was higher with sorafenib (21 vs. 9 months), but there was no difference in OS. A nonsignificant difference in EFS was noted in patients with FLT3 mutations (18 vs. 6 months). However, there was a significantly higher risk of hand–foot syndrome, diarrhea, and cardiac events in the sorafenib group.[53] Updated analysis published in 2021 after a median follow-up of 78 months demonstrated the sorafenib arm to have a higher EFS (41 vs. 27%) and relapse-free survival (53 vs. 36%) without any OS advantage (5-year OS 63 vs. 51%).[54]

The evaluation of sorafenib's effectiveness in a patient population with a high prevalence of FLT3 mutations has solely relied on a retrospective study encompassing 183 patients, with a median age of 52 years. Patients were compared based on whether the initial therapy was intensive chemotherapy alone or with sorafenib. After propensity matching, addition of sorafenib demonstrated a higher ORR (99 vs. 83%), similar rates of CR (79 vs. 74%), and a higher OS (42 vs. 13 months). As most of the above studies have not shown a uniform clinical benefit in a prospective setting, sorafenib is currently not approved for routine use in AML. Prospective studies including patients enriched for FLT3 mutations are expected to provide a clearer picture of its clinical efficacy.

Sorafenib is presently undergoing evaluation as an integral component of standard therapy for patients who have recently been diagnosed (NCT05404516) and as an adjunct to conditioning in the context of stem cell transplantation (NCT03247088).

Midostaurin

Midostaurin, classified as a first-generation multikinase inhibitor, exhibits inhibitory effects on FLT3, vascular endothelial growth factor receptor-2, c-kit, platelet-derived growth factor receptor-α (PDGFRα), and PDGFRβ. The clinical efficacy of midostaurin was demonstrated in a phase 2 trial involving a cohort of 20 patients diagnosed with FLT3-mutated AML or high-risk MDS. When administered as a standalone treatment, midostaurin exhibited noteworthy clinical activity, resulting in a substantial decrease in both blood and marrow blast counts.[55] Similar to sorafenib, most further studies evaluated midostaurin as part of combination therapy. The safety profile of midostaurin in conjunction with intensive chemotherapy was evaluated in a phase 1b trial involving 40 newly diagnosed patients below the age of 60, of whom 13 exhibited FLT3 mutations. The trial encompassed three distinct dosing schedules for midostaurin, and the results demonstrated a favorable safety profile. Importantly, midostaurin achieved a complete response in 92% of patients with FLT3 mutations, while maintaining an acceptable level of safety.[56]

Based on these data, it was evaluated in a phase 3 trial (RATIFY) that randomized 717 patients with FLT3 mutation at diagnosis to receive intensive chemotherapy alone or with midostaurin.[57] Initial rate of CR was similar with addition of midostaurin (58 vs. 53.5%) with median time to CR of 35 days. After a median follow-up of 59 months, OS was higher in the midostaurin group (74 vs. 25.6 months) with a 4-year OS of 51 versus 44%. However, several concerns were identified with this trial, which warrant further consideration.[58] For instance, the median age of patients with FLT3 mutations in this trial was much younger compared with published data and the study population was unusually enriched for FLT3-TKD mutations (22% compared with 5–6% in general). Patients with FLT3-TKD mutations, which do not result in worse prognosis compared with wild type FLT3, also

experienced significant clinical benefit from midostaurin. This finding supports the approval of midostaurin by the FDA in 2017 for newly diagnosed patients with FLT3-mutated AML, as it demonstrates the efficacy of the treatment across different FLT3 mutation subtypes.

It is essential to remember that midostaurin has no significant activity in patients with relapsed/refractory AML with preclinical studies only documenting "blast reduction" with no durable response.[59] Ongoing studies are currently assessing the efficacy of midostaurin in combination with gemtuzumab (NCT03900949, NCT04385290) and CPX-351 (NCT04982354) as part of the treatment regimen for newly diagnosed patients. These trials aim to further explore the potential benefits of incorporating midostaurin into combination therapies and expand our understanding of its effectiveness in different treatment approaches.

Concomitant use of posaconazole or voriconazole is associated with a significant rise in downstream metabolites and a 1.4-fold rise in drug exposure.[60] However, no clear effect on excessive toxicity has been observed, except a possible correlation with pulmonary toxicity initially noted in the RATIFY trial. In this trial, no dose reduction was specified, and a subsequent analysis observed that a higher-dose intensity was associated with higher clinical benefit without any increase in toxicity.[61] Thus, the current recommendation is to continue the drug at full dose along with azoles while closely watching for pulmonary complications to achieve maximal efficacy.[62]

Second-Generation FLT3 Inhibitors

Nondurability of clinical response and limited single-agent activity are important limitations of first-generation FLT3 inhibitors. Use of FLT3 inhibitors is also fraught with development of resistance mediated by secondary mutations in either FLT3-TKD or other related genes including *NRAS* and *AXL*, which allow a proliferative signal even in the presence of FLT3 inhibitors.[63] Second-generation FLT3 inhibitors were developed with an intention to overcome these limitations and provide better efficacy as monotherapy.

Quizartinib

Quizartinib (AC-220) was the first compound selectively designed to inhibit mutant FLT3-ITD with high potency and specificity, intended to overcome limitations of first-generation drugs.[64] Quizartinib underwent its initial evaluation in a phase I trial that enrolled 76 patients with relapsed AML who had experienced treatment failure following a median of three prior therapies, irrespective of their FLT3 mutation status. The primary objective of the trial was to assess the safety and tolerability of quizartinib in this specific patient population. The study aimed to gather preliminary data on the efficacy and potential therapeutic benefits of quizartinib as a treatment option for relapsed AML patients who had exhausted multiple prior therapies. ORR was 30%, with higher responses in the FLT3-ITD-mutated subset, with a median OS of 14 weeks. The most common dose-limiting serious adverse event was QT prolongation, noted in 12% of the population.[65]

The efficacy of quizartinib was subsequently evaluated in a phase 2 trial, specifically as a monotherapy, in a cohort of 333 patients with relapsed or refractory AML.[66] The study group was divided into two cohorts, first >60 years who progressed within 1 year of first-line therapy and second >18 years of age who received at least one salvage after progression. The rate of composite CR (CRc) in patients with FLT3 mutations in the first cohort was 56% and in the second was 46%. QTc prolongation was noted in 10% of patients.

The efficacy of quizartinib was assessed in a phase 3 trial known as QUANTUM-R, which specifically targeted patients with relapsed or refractory AML harboring FLT3-ITD mutations. In this trial, a total of 367 patients were randomly assigned to receive either quizartinib alone or salvage chemotherapy, with a ratio of 2:1.[67] The rate of CRc in the quizartinib group was 48% and chemotherapy group was 27%. Median time to first CRc was 4.9 weeks for quizartinib. After a median follow-up of 23.5 months (interquartile range: 15–32), median OS was higher with quizartinib (6.2 vs. 4.7 months, $p = 0.02$). Grade 3 QTc prolongation was present in 4% of patients in the quizartinib arm. Although this survival advantage may not be clinically significant, this trial demonstrated the feasibility of monotherapy with an oral drug in the relapsed/refractory setting.

Recently, data on front-line use of quizartinib was presented at the EHA 2022 meeting (Quantum-First study, EHA Abstract Erba H. 356965). A total of 539 patients were initiated on standard intensive chemotherapy and randomized to additionally receive quizartinib or placebo. Initial CR rates were similar (71 vs. 64%), although there was an increased risk of neutropenia with quizartinib. After a median follow-up of 39.2 months, OS was longer in the quizartinib arm (31.9 vs. 15 months). After censoring for hematopoietic stem cell transplantation, a trend to longer OS with quizartinib was observed (HR = 0.752; 95% CI = 0.56–1.008). These data led to accelerated regulatory approval of quizartinib as first-line therapy for newly diagnosed patients with FLT3-ITD mutations. Further studies of quizartinib in combination with idarubicin/cytarabine and cladribine (NCT04047641) and with azacytidine/venetoclax (NCT04687761) are currently underway.

Quizartinib is also metabolized by hepatic enzymes, and a 2-fold rise in maximal concentration and AUC is noted on concomitant use of azoles (except fluconazole).[68] A dose-dependent increase in the risk of QTc prolongation is noted, and dose reduction is recommended when using with concomitant strong CYP3A4 inhibitors such as posaconazole and voriconazole.[69]

Gilteritinib

Gilteritinib, a small molecule inhibitor of FLT3 and multiple kinases (FLT3-ITD, FLT3-TKD, c-Kit, ALK, and AXL), exhibits potent and long-lasting inhibitory effects, particularly against FLT3-ITD. Its inhibitory activity surpasses that of first-generation inhibitors, suggesting superior efficacy.[70] Inhibition of AXL and FLT3-TKD is clinically relevant due to their role in mediating secondary resistance to FLT3 inhibitor therapy.[71]

Safety and dosing of gilteritinib was established in a phase 1/2 study including 252 patients with relapsed/refractory AML. More than 90% inhibition of FLT3 signaling was observed with an ORR of 40%.[72] The most common toxicity was diarrhea and elevated liver enzymes. Further follow-up of these data indicated an ORR of 49% in patients with mutated FLT3. Patients who received a daily dose of >80 mg exhibited a median response duration of 20 weeks, accompanied by a median OS of 31 weeks.[73]

The promising efficacy observed as a single agent prompted the initiation of the phase 3 ADMIRAL trial. This trial involved the randomization of 371 patients with relapsed/refractory AML to receive either gilteritinib alone or salvage chemotherapy.[74] FLT3-ITD mutations were present in 88.4% of the overall cohort. CRc rate with gilteritinib was 54.3% compared with 21% with salvage chemotherapy (HR = 32.5; 95% CI = 22.3–44). Median OS with gilteritinib was 9.3 versus 5.6 months (HR for death = 0.64; 95% CI = 0.49–0.83). A higher proportion of patients received an allogeneic transplant in the gilteritinib arm (25 vs. 15%), but a survival advantage was maintained after censoring at the time of transplant. Importantly, equivalent efficacy was also maintained in patients with a FLT3-TKD mutation.

Long-term data from this trial were recently published in June 2022 with a median follow-up period of 37 months. As most relapses occurred in the first 18 months, OS at the end of follow-up was similar to data from the ADMIRAL trial. Two-year survival probability was higher with gilteritinib (20.6 vs. 14.2%). Serious adverse events were noted in 20.3% of patients receiving gilteritinib, the most common being elevated liver enzymes followed by cardiac events.[75] Although this study highlighted maximal clinical benefit for patients with FLT3-ITD high allelic ratio, a uniform benefit irrespective of FLT3-ITD allelic ratio and presence of comutations was confirmed in a subsequent analysis.[76] Based on these data, gilteritinib received regulatory approval for patients with relapsed/refractory AML with FLT3 mutations.

Gilteritinib was also evaluated recently in newly diagnosed patients with mutated FLT3 in a phase 3 trial (LACEWING study) in which 123 patients were randomized 1:1:1 to receive azacytidine alone, gilteritinib alone or both in combination.[77] Despite higher response rates (58.1 vs. 26.5%) and similar toxicity, no OS benefit was observed with combination therapy and the study was prematurely terminated.

Notable ongoing studies include gilteritinib in combination with venetoclax and azacytidine for newly diagnosed patients (NCT05520567), a head to head comparison with midostaurin (NCT04027309) and in combination with a Syk inhibitor lanraplenib for relapsed disease (NCT05028751).

Gilteritinib is also metabolized by the CYP3A4 enzyme system, and an increased AUC is observed when used concomitantly with azoles.[78] However, no dose reduction is currently recommended as no increase in clinical toxicity has been observed.[33]

Crenolanib

Crenolanib is a quinolone derivative initially developed as a PDGFR-α/β inhibitor targeting various solid tumors.[79] It's potential antileukemic properties were observed in vitro using a xenograft mouse model in 2013 with documentation of significant FLT3-ITD inhibition. Importantly, it was active against several FLT3-TKD (except F691L) mutations, which confer resistance to FLT3 inhibitor therapy, indicating a role in pretreated patients.[80,81]

Crenolanib was evaluated in a phase 2 study including 38 patients following a median of 3.5 prior lines of therapy, of which 13 were tyrosine kinase inhibitor (TKI) naïve and 21 had received previous TKI.[82] Among TKI-naïve patients, CRi + multiple layers file sharing system (MLFS) of 31% was observed, compared with 5% of those who had received previous TKI. Patients with CRi/MLFS had higher EFS (median: 22 vs. 8 weeks, $p = 0.003$) and OS (55 vs. 15 weeks, $p = 0.166$) with acceptable toxicity.

Efficacy in relapsed/refractory disease in combination with azacytidine or salvage chemotherapy was published in 2018 in a phase 2 study enrolling 28 patients, of which 20 received crenolanib with intensive chemotherapy and eight with azacytidine. ORR was 46%, with four patients achieving MRD negativity. Median OS was 4.7 months (range, 0.4–27 months) with no significant grade 3/4 adverse events.[83] Both of the aforementioned studies demonstrated the efficacy of crenolanib in relapsed/refractory AML. Intriguingly, among the patients who experienced disease progression while on crenolanib, resistance to treatment was observed to be driven by non-FLT3-dependent mechanisms, such as the emergence of secondary mutations in NRAS and IDH2.[84]

Crenolanib is recently being evaluated in newly diagnosed patients in combination with standard therapy. In a phase 2 study, 29 newly diagnosed FLT3-mutated patients were treated with intensive chemotherapy in combination with crenolanib and demonstrated MRD negativity in 80% of patients at the end of induction.[85] Long-term results of the trial were presented in the 2022 ASCO meeting and included data from 44 patients. With a median follow-up of 45 months, median OS was not reached and median EFS was 45 months.[86] Ongoing phase III trials include the comparison of crenolanib with midostaurin as a follow-up therapy after initial treatment (NCT03258931) and the evaluation of crenolanib in combination with intensive chemotherapy for relapsed/refractory patients (NCT03250338).

►**Tables 1** and **2** provide a summary of key trial results and important characteristics of the mentioned drugs, respectively, specifically focusing on drug administration

A Primer on Resistance to Targeted Oral Agents

With accumulating data on disease progression on targeted oral agents, several molecular mechanisms of resistance have emerged. In case of IDH1 inhibitors, both primary and secondary resistance to therapy may be noted.[87] Occurrence of oncogenic comutations in *DNMT3A*, *NPM1*, *ASXL1*, *SRSF2*, and *NRAS* and receptor tyrosine kinase pathway are associated with primary resistance to IDH1 inhibitors. Secondary resistance is mediated by either the emergence of new IDH2 mutations or alternate site IDH1 mutations (the

Table 1 Key evidence for FLT3 and IDH1/2 inhibitors showing clinical efficacy

Drug	Key study showing efficacy	*N*	Type	Clinical setting	Clinical use	Major finding	Regulatory approval received
Sorafenib	SORAML	276	Phase 2	Newly diagnosed AML	Combination with IC	Higher EFS (21 vs. 9 mo), similar CR and OS	No
Midostaurin	RATIFY	717	Phase 3 RCT	Newly diagnosed AML with FLT3-ITD	Combination with IC	Median OS 74 vs. 25 mo	Yes
Quizartinib	Quantum-FIRST	539	Phase 3 RCT	Newly diagnosed AML with FLT3-ITD	Combination with IC	Median OS 31 vs. 15 mo	Yes
Gilteritinib	ADMIRAL	247	Phase 3 RCT	Relapsed/refractory AML with IDH1 mutations	Monotherapy vs. salvage chemotherapy	Median OS 9.3 vs. 5.6 mo	Yes
Crenolanib	Wang et al, 2022[77]	44	Phase 2	Newly diagnosed AML with FLT3-mutated	Combination with IC	Median OS NR, median EFS 45 mo	No
Ivosidenib	AGILE	146	Phase 3 RCT	Newly diagnosed AML with IDH1 mutation	Combination with azacytidine	Median OS 24 vs. 7.9 mo	Yes
Enasidenib	IDHentify	319	Phase 3 RCT	Relapsed/refractory AML with IDH2 mutations	Monotherapy	Higher ORR (41 vs. 11%) and CR (26 vs. 3%), similar OS	Yes
Olutasidenib	–	153	Phase 2	Relapsed/refractory AML with IDH1 mutations	Monotherapy	ORR 48%, CR + CRi 35%, median OS 11.7 mo	Yes

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; EFS, event-free survival; FLT3, FMS like tyrosine kinase 3; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; NR, not reported; ORR, overall response rate; OS, overall survival; RCT, randomized controlled trial.

Table 2 Salient details of clinical use of FLT3 and IDH1/2 inhibitors in acute myeloid leukemia

Drug name	Common dose used	Monotherapy/ combination	Important nonhematologic toxicities
Sorafenib	400 mg twice a day on D10 to 19 of induction	Combination with IC	Diarrhea (10% with Gd 3) and hand foot syndrome (7% with Grade 3)
Midostaurin	50 mg twice a day from D8 to D21 of induction	Combination with IC	Anemia, thrombocytopenia, skin rash/desquamation (14%)
Quizartinib	40 mg once a day from D8 to D21 of induction	Combination with IC	Neutropenia, QT prolongation (2.3% Grade 3)
Gilteritinib	120 mg once a day	Monotherapy	Febrile neutropenia, thrombocytopenia
Crenolanib	100 mg TID from D8 of induction	Combination with IC	Diarrhea (18% with Gd 3)
Ivosidenib	500 mg once a day	Combination with IC	Differentiation syndrome (14%)
Enasidenib	100 mg once a day	Monotherapy	Differentiation syndrome (13%), hyperbilirubinemia (26%)

Abbreviations: FLT3, FMS like tyrosine kinase 3; Gd, grade; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; TID, three times a day.

most common, R132-S280F), which restore intracellular concentrations of 2-hydroxyglutarate (2-HG).[88] Similarly, acquired transmutations in IDH2 restore 2-HG levels leading to clinical resistance to enasidenib.[89] These mutations are present in active enzyme sites (including R132 in IDH1 and R140/R172 in IDH2) and significantly increase the IC50 required for enzyme inhibition, leading to resistance to therapeutically achieved concentrations.[87]

Secondary IDH1 mutations can be overcome using newer IDH1 inhibitors, including IDH224, FT-2102, and DS1001B, which strongly bind to the mutated enzyme despite secondary mutations. This provides a potential to shift to alternate IDH1 inhibitors after failure of first-line therapy.[90]

Similarly, primary resistance to FLT3 inhibitors is known to be mediated by the site of FLT3-ITD mutations, each of which confer differing sensitivities to enzyme inhibition. Resistance is also mediated by the tumor microenvironment, where FLT3-mutated leukemia stem cells are protected and high CYP3A4 activity reduces local drug exposure.[91,92] Secondary resistance is mediated by either mutations in alternate signaling pathways or selection of clones with resistance conferring FLT3 mutations.[93] Similar mechanisms are active in case of quizartinib.[94] In contrast, resistance to gilteritinib and crenolanib is mediated by mutations in alternate genes, including *NRAS* and *IDH2*, implying the need for alternate approaches to overcome the same.[95]

Risk of Infections with Targeted Agents

It is vital to consider the risk of infections when using targeted agents, especially in the context of relapsed/refractory disease and in combination with other chemotherapeutic agents. The incidence of infectious complications associated with targeted agents can be estimated based on data from initial clinical trials. However, it is important to note that these complications may be reported variably as "infections," "febrile neutropenia," or "fever." The occurrence of these complications is contingent upon whether the drug is administered as monotherapy, in combination with chemotherapy, or in a posttransplant setting. ►**Table 3** provides a summary of these findings. Guidelines on the same were recently published by a multiple European societies in a joint venture.[96]

IDH1/2 Inhibitors

No specific increase in infectious complications have been noted with these agents. In initial trials of these agents as monotherapy, pulmonary infections were noted in 15 to 20% of patients, similar to other settings in AML. It must be noted that a higher risk of Clostridial infections was noted on combination with intensive chemotherapy in the initial phase 1 study with IDH1/2 inhibitors but has not been observed elsewhere.[30]

FLT3 Inhibitors

A recent clinical guideline assessed the risk of infections with midostaurin. The median incidence of febrile neutropenia was 35% and pneumonia was 9%, with sepsis ranging from 4 to 18%.[96] No excess risk of fungal or viral infections was observed. With quizartinib, the risk of sepsis as monotherapy was similar to salvage chemotherapy, with a slightly higher risk of pneumonia, warranting close monitoring.

Discussion

Intensive chemotherapy and stem cell transplantation may not be feasible (advanced age, reduced fitness, or logistic barriers) or effective (relapsed / refractory disease) in certain settings with AML.[8,97] In this setting, the combination of venetoclax with HMAs has significantly improved initial response rates and survival.[97,98] However, drug development for AML has lagged behind other hematologic malignancies and availability of targeted oral inhibitors represents the next important step forward in the treatment of AML.

Limitations

The limitations of this review lie in its narrative nature and lack of systematic literature selection and analysis,

Table 3 Overall incidence of infections in pivotal trials compared with placebo when used with intensive chemotherapy, low-dose therapy/monotherapy, or posttransplant maintenance

	Targeted agent combined with chemotherapy		Targeted agent used as monotherapy		Targeted agent in posttransplant setting	
	Infections in drug arm	Infections in control arm	Infections in drug arm	Infections in control arm	Infections in drug arm	Infections in control arm
	SORAML				SORMAIN	
Sorafenib	55%	48%	N/A	N/A	26.2%	23%
	RATIFY				NCT01477606	
Midostaurin	52%	50%	N/A	N/A	56%	–
	Quantum first		Quantum-R			
Quizartinib			31%	28%	–	–
	LACEWING		ADMIRAL			
Gilteritinib	35.6%	21.3%	46.7%	36.7%	–	–
	AGILE		NCT02074839			
Ivosidenib	28%	34%	18%	N/A	–	–
	AG221-AML-005		IDHENTIFY			
Enasidenib	37%	25%	2.5%	12.1%	–	–

Abbreviation: N/A, not applicable.

potentially introducing bias in the included studies. Without a predefined search strategy and inclusion criteria, certain studies may be overlooked, affecting the validity of findings.

Generalizability and Future Perspectives

The findings of our narrative review on FLT3 and IDH1/2 inhibitors in AML should be interpreted in the context of drug availability and regional differences. Although our review focused on both FLT3 and IDH1/2 inhibitors, it is important to note that only FLT3 inhibitors are currently available in India, while the availability of other inhibitors may vary worldwide. This limitation may affect the generalizability of our findings to regions where IDH1/2 inhibitors are commonly used in clinical practice. Additionally, variations in drug approval processes, treatment guidelines, and health care infrastructure across different countries can further influence the applicability of our findings. Therefore, caution should be exercised when extrapolating the results of our review to patient populations in regions where specific inhibitors are not available or where treatment practices differ. Further studies and collaborations across different regions are warranted to validate the efficacy and safety of IDH1/2 inhibitors in AML beyond the scope of our current review.

Conclusion

Drug therapy for AML is a field of active development, and several drugs with novel mechanisms including venetoclax, glasdegib, SYK, and menin inhibitors under evaluation.

The ultimate aim of targeted therapy for AML is the use of continuous low-toxicity regimens with a high response rate (similar to chronic myeloid leukemia) to improve survival for in this difficult to treat disease.

Patient Consent
None declared.

Funding
None declared.

Conflict of Interest
None declared.

Acknowledgment
The authors express their gratitude to Dr. Akriti Arora for her valuable contribution in typesetting and enhancing the grammar of the manuscript.

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The Effect of Chemotherapeutic Agents on Survival in Metastatic Non-Small-Cell Lung Cancer with KRAS Mutation

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Ind J Med Paediatr Oncol 2024;45:127–133.

Abstract

Introduction *KRAS* mutation is observed in up to 30% of non-small-cell lung cancer (NSCLC) cases and is corelated with a poor prognosis. In the cases with *KRAS* p.G12C mutation and first-line chemotherapy (± immunotherapy) resistance, a targeted drug option is available.

Objectives Our study aimed to examine the correlation between first-line chemotherapy agents and treatment response in patients with KRAS-mutated metastatic NSCLC.

Materials and Methods Retrospective database searches were performed on cases diagnosed with metastatic NSCLC at our center between January 2019 and December 2021 that were found to be KRAS mutation positive using the *next-generation sequencing* (NGS) approach. The cases were classified into five subgroups based on the chemotherapy regimens (platinum + gemcitabine, platinum + taxane, platinum + pemetrexed, platinum + vinorelbine, and others). The clinical and demographic data of 41 cases were analyzed retrospectively, and survival analyses were performed using the Kaplan–Meier method.

Results Thirty-seven of 41 patients (90.2%) were males, and 27 (65.9%) had adenocarcinoma histology. The most prevalent mutation was KRAS G12C, with 12 cases (29.2%), followed by KRAS G12V, with 9 cases (21.9%). Other mutations were as follows: KRAS G12D 4 (9%), KRAS G13C 3 (7.3%), KRAS G12A 2 (4.8%), KRAS G12R 2 (4.8%), KRAS Q61H 2 (4.8%), KRAS Q61L 2 (4.8%), KRAS V14I 2 (4.8%), KRAS A146T 1 (2.4%), KRAS G13G 1 (2.4%), and KRAS G1C 1 (2.4%). The median progression-free survival (mPFS) for all groups was 4.6 months (95% confidence interval [CI]: 2.7-6.5), and there were no statistically significant differences between the groups ($p = 0.121$). The median overall survival (mOS) for all groups was 9.3 months (95% CI: 3.8–14.5), and there were no statistically significant differences between the groups ($p = 0.805$).

Keywords
- metastatic NSCLC
- KRAS
- chemotherapy
- OS
- PFS
- platinum

article published online
September 27, 2023

DOI https://doi.org/10.1055/s-0043-1775800.
ISSN 0971-5851.

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Conclusions OS and PFS analyses showed no differences between platinum + taxane, platin + pemetrexed, platinum + gemcitabine, and platin + vinorelbine used in first-line treatments for KRAS mutant NSCLC cases. We believe that patient-specific characteristics may be a determining factor in selecting chemotherapy for this patient population.

Introduction

Lung cancer causes approximately 1.8 million deaths annually worldwide.[1] Despite the increase in screening programs, the improvement of surgical techniques, and the use of targeted therapies and immunotherapies, lung cancer is the most common cause of cancer-related death.[2,3] The disease stage is the most significant indicator of prognosis, with 5-year survival rates less than 10%.

Before selecting a course of treatment in metastatic cases, it is recommended that ALK and ROS 1 rearrangement, BRAF V600E mutation, EGFR mutation, HER2 mutation, KRAS mutation, METex14 mutation, NTRK gene fusion, and RET rearrangement, programmed death ligand 1 (PDL-1) expression be analyzed as predictive biomarkers in treatment.[4]

The RAS oncogene family includes the *KRAS*, *NRAS*, and *HRAS*. KRAS is a G-protein in MAP/ERK pathway with GTPase activity. In the activated KRAS mutation, intracellular signaling pathways are activated. It is observed in up to 30% of NSCLC cases, primarily in adenocarcinoma subtypes. Mutations are frequently detected at codons 12, 13, 61.[5–7] The presence of the KRAS oncogene is related to a poor prognosis and unresponsiveness to EGFR *tyrosine kinase inhibitors* treatment.[8–10] Sotorasib is a Food and Drug Administration (FDA) approved treatment option for cases with the KRAS p.G12C mutation that were diagnosed with non-small-cell lung cancer (NSCLC). Sotorasib is recommended by the National Comprehensive Cancer Network (NCCN) guideline version 5.2022 as a treatment option in metastatic cases unresponsive to platinum-based chemotherapy (±immunotherapy).[11] There are cell culture and clinical studies revealing that KRAS mutations may play role in the treatment of NSCLC cases.[5,12] In metastatic NSCLC patients with KRAS mutation, targeted therapies are used in those who have progressed after first-line chemotherapy. Systemic chemotherapy in first-line treatment still maintains its importance today. There are different chemotherapy protocols that can be used in metastatic NSCLC patients. In our study, we aimed to investigate the chemotherapeutic agents used in metastatic NSCLC patient with KRAS mutation and whether there is a relationship between these agents and survival.

Materials and Methods

Patients

Patients with metastatic NSCLC with KRAS mutation diagnosed and followed up in our center, between January 2019 and December 2021, were evaluated retrospectively. The data of the patients accessed through the hospital electronic automation system and patient files were recorded. Patient demographics, histopathological features, disease stage at diagnosis, next-generation sequencing (NGS) test results, PDL-1 levels, palliative treatment history, chemotherapy protocols, date of diagnosis, date of progression, and date of death were recorded.

Inclusion Criteria

The inclusion criteria were determined as follows: being older than 18, not having received chemotherapy in the past, being diagnosed with metastatic disease, not having undergone curative radiotherapy or surgery, and not having a positive driver mutation.

Exclusion Criteria

The exclusion criteria were determined as follows: patients with unknown mutation status, patients with positive EGFR or ALK mutations, patients with no follow-up data, patients without metastatic stage, patients who underwent curative radiotherapy, and surgical treatment. A total of 667 lung cancer cases were evaluated with the NGS technique; RAS mutation was detected in 66 patients. After applying the inclusion and exclusion criteria, the data of 41 cases were analyzed in total. Parameters for progression-free survival (PFS) and overall survival (OS) were generated based on the clinical and demographic characteristics and chemotherapeutic agents employed in the treatment. The platinum group of chemotherapeutic medicines consisted of carboplatin and cisplatin, and the taxane group of medicines consisted of docetaxel and paclitaxel. The primary endpoint of the study was to explore the relationship between chemotherapy protocols and OS and PFS. The secondary endpoint was to explore the mutation subtypes of the patient population and the chemotherapy options preferred in patients. For KRAS mutation analysis, the QIAseq Solid Tumor Custom Panel was utilized, and somatic mutation analyses were conducted by performing mutation studies in genes using the NGS method.

Statistical Method

The cases were classified into five subgroups based on the chemotherapy regimens they received: platinum + gemcitabine, platinum + taxane, platinum + pemetrexed, platinum + vinorelbine, and others. In the survival analyses for these subgroups, the Kaplan–Meier analysis was performed. Statistical significance was accepted as $p < 0.05$.

Table 1 Demographic and clinical characteristics of cases

Variable		*n* (%)
Gender	Female	4 (9.8)
	Male	37 (90.2)
Age (y), mean (minimum–maximum)		65.2 (47–81)
Histology	Adenocarcinoma	27 (65.9)
	Squamous	4 (9.8)
	NOS	10 (24.4)
Stage	4	41 (100)
Performance status pretreatment	ECOG 0	6 (14.6)
	ECOG 1	9 (21.9)
	ECOG 2	26 (63.5)
	ECOG 3	0 (0)
	ECOG 4	0 (0)
KRAS mutation	KRAS G12C	12 (29.2)
	KRAS G12V	9 (21.9)
	KRAS G12D	4 (9)
	KRAS G13C	3 (7.3)
	KRAS G12A	2 (4.8)
	KRAS G12R	2 (4.8)
	KRAS Q61H	2 (4.8)
	KRAS Q61L	2 (4.8)
	KRAS V14I	2 (4.8)
	KRAS A146T	1 (2.4)
	KRAS G13G	1 (2.4)
	KRAS G1C	1 (2.4)
Other common mutations	BRCA-1	7 (17)
	BRCA-2	5 (12)
	TP53	2 (4.8)
	BRAF V600E	1 (2,4)
	NTRK 1	2 (4.8)
	PIK3CA	2 (4.8)
	PTEN	1 (2,4)
	MET amplification	3 (7.3)
Metastasis site	Liver	6 (14.6)
	Lung	9 (21.9)
	Brain	6 14.6)
	Bone	14 (34.1)
	Adrenal gland	9 (21.9)
NGS studied tissue	Lung	18 (51.4)
	Lymph node	3 (8.6)
	Blood	4 (11.4)
	Brain	3 (8.6)
	Bone	4 (11.4)
	Adrenal gland	2 (5.7)

(*Continued*)

Table 1 (*Continued*)

Variable		*n* (%)
	Pleura	2 (5.7)
PDL-1 staining (mean)		16.4 (0–97)
Palliative surgery		1 (2.4)
Palliative radiotherapy		13 (31.7)
Chemotherapy protocols	Platinum + taxane	24 (58)
	Platinum + pemetrexed	6 (14.6)
	Platinum + gemcitabine	4 (9.7)
	Platinum + vinorelbine	3 (7.3)
	Platinum	2 (4.9)
	Taxane	1 (2.4)
	Vinorelbine	1 (2.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; NGS, next-generation sequencing; NOS, not otherwise specified; PDL-1, Programmed death-ligand 1.

Ethics

Karadeniz Technical University (KTU) Faculty of Medicine Ethics Committee (April 29, 2022, numbered 24237859-323) approved the study. All stages of our work were carried out in accordance with the 1964 Helsinki Declaration and its later amendments. Since our study was retrospective, the ethics committee did not request informed consent from the subjects.

Results

The data from 41 cases with metastatic NSCLC who tested positive for the KRAS mutation were analyzed retrospectively. The study population included of 37 males (90.2%) and 4 females (9.8%). The mean age of the patients was 65.2 (47–81 years). Histologically, adenocarcinoma was the most prevalent kind at 27 (65.9%) cases, followed by squamous with 4 (9.8%) cases and NOS with 10 (24.4%) cases. All cases had a metastatic disease at diagnosis. KRAS mutation locations were detected as follows: KRAS G12C in 12 (29.2%) cases, KRAS G12V in 9 (21.9%) cases, KRAS G12D in 4 (9%) cases, KRAS G13C in 3 (7.3%) cases, KRAS G12A in 2 (4.8%) cases, KRAS G12R in 2 (4.8%) cases, KRAS Q61H in 2 (4.8%) cases, KRAS Q61L in 2 (4.8%) cases, KRAS V14I in 2 (4.8%) cases, KRAS A146T in 1 (2.4%) case, KRAS G13G in 1 (2.4%) case, and KRAS G1C in 1 (2.4%) case. In nearly half of the cases (51.4%), the NGS test was performed on lung tissue. Chemotherapy preferences were as follows: platinum + taxane in 24 (58%) cases, platinum + pemetrexed in 6 (14.6%) cases, platinum + gemcitabine in 4 (9.7%) cases, platinum + vinorelbine in 3 (7.3%) cases, platinum in 2 (4.9%) cases, taxane in 1 (2.4%) case, and vinorelbine in 1 (2.4%) case.

Demographic and clinical data of the cases are presented in ►**Table 1**. The mean OS (mOS) at 95% confidence interval (CI) was determined as 8.9 months (6.2–11.5) for the platinum + taxane group, as 5.4 months (–) for the platinum + pemetrexed group, as 14.3 months (3.2–25.3) for the platinum + gemcitabine group, as 19.2 months (–) for the platinum + vinorelbine group, and as 8.4 months (0–17.9) in other cases. The overall mOS was 9.3 months (3.8–14.5) in all groups at 95% CI, and there was no statistically significant difference in the mOS values between the groups ($p = 0.805$). The mean PFS (mPFS) at 95% CI was determined as 3.5 (1–5.9) for the platinum + taxane group, as 1.3 (0–3.0) for the platinum + pemetrexed group, as 8.0 (1.8–14.2) for the platinum + gemcitabine group, as 10.5 (0–27) for the platinum + vinorelbine group, and as 2.1 (0.7–3.4) in other cases. The overall mPFS for all groups was 4.6 (2.7–6.5) at 95% CI, and there was no statistically significant difference in the mPFS values between the groups ($p = 0.121$; ►**Table 2**). ►**Fig. 1** depicts the OS Kaplan–Meier curve, while ►**Fig. 2** depicts the PFS curve.

Discussion

In treating metastatic NSCLC, the level of PDL-1, the existence of driver mutations, the number of metastatic sites, histological subtype, tumor load, and rate of disease progression serve as a guide for clinicians. Due to the survival benefits of targeted agents and immunotherapy, molecular tests for driver mutations and screening for immunological biomarkers are recommended in all cases by the guidelines.[13–15]

In the cases with no mutation that can be treated with targeted therapy in metastatic NSCLC, treatment with a combination of chemotherapy and immunotherapy or immunotherapy alone may be considered.[16,17] There are different alternative combination treatments available in chemotherapy options. Chemotherapy regimens based on platinum have been revealed to be superior to those based on platinum-free chemotherapy. The effectiveness of pemetrexed in nonsquamous histology is well established.[18,19] Moreover, it has been established that the addition of bevacizumab to doublet platinum-based regimens significantly improves OS and PFS.[20]

KRAS is the most common mutation and more prevalent in smokers with NSCLC. It causes mutations in codon 12 most

Table 2 The relationship between chemotherapy and OS-PFS

Chemotherapy protocols, *n* (%)	Median OS, mo (95% CI)	Median PFS, mo (95% CI)
Platinum + taxane: 24 (58)	8.9 (6.2–11.5)	3.5 (1.0–5.9)
Platinum + pemetrexed: 6 (14.6)	5.4 (–)	1.3 (0–3.0)
Platinum + gemcitabine: 4 (9.7)	14.3 (3.2–25.3)	8.0 (1.8–14.2)
Platinum + vinorelbine: 3 (7.3)	19.2 (–)	10.5 (0–27)
Others: 4 (9.7)	8.4 (0–17.9)	2.1 (0.7–3.4)
Overall	9.3 (3.8–14.5)	4.6 (2.7–6.5)
Log-rank test (*p*)	0.805	0.121

Abbreviations: Cl: confidence interval; OS: overall survival; PFS: progression-free survival.

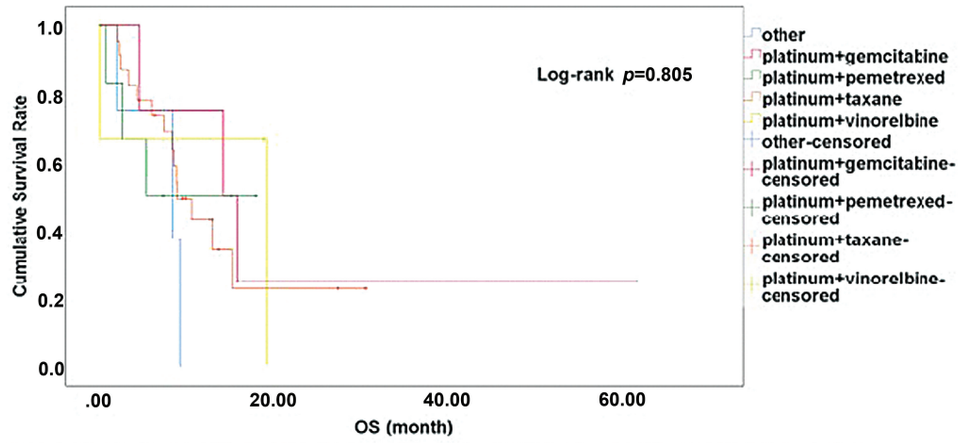

Fig. 1 The Kaplan–Meier curve shows the relationship between chemotherapy and overall survival (OS).

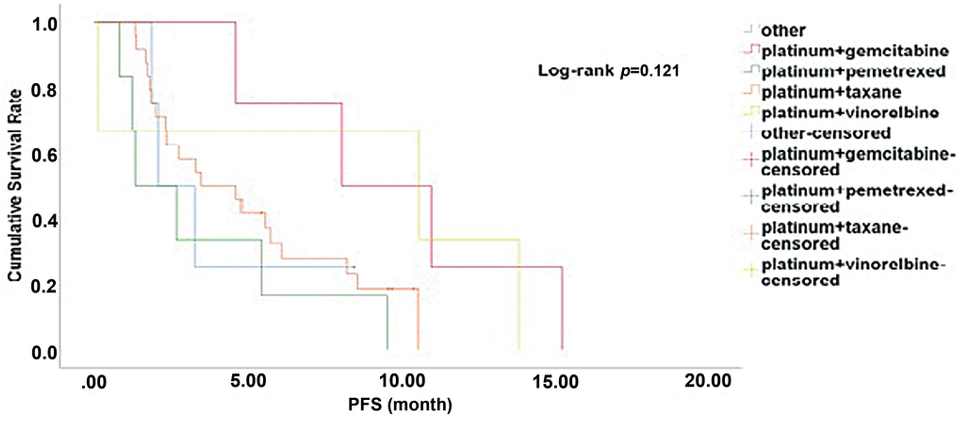

Fig. 2 The Kaplan–Meier curve shows the relationship between chemotherapy and progression-free survival (PFS).

frequently (95%), and mutations occur in the G12C, G12V, and G12D loci, in that order.[21,22] This mutation has been found to have a negative effect on survival in patients with NSCLC treated with platinum-based regimens.[23] Advanced NSCLC patients with KRAS p.G12C mutation and prior chemotherapy ± immunotherapy had an mPFS of 6.8 months (95% CI: 5.1–8.2) and an mOS of 12.5 months (95% CI: 10.0–could not be evaluated) had with the use of Sotorasib.[11] In a separate study, it was found that 39 KRAS mutant NSCLC cases caused a numerical decrease in OS and PFS when compared to 69 KRAS wild NSCLC cases. While the difference in survival was not significant, it was observed that the frequency of aggressive disease course and liver and brain metastases increased.[24]

In light of the current data, the aim of our study was to explore the contribution of chemotherapy selection to survival of all patients with a KRAS mutation in the first-line chemotherapy selection, given that guidelines only recommend the use of a KRAS inhibitor in cases involving a KRAS G12C mutation in the second-line treatment.

In a multicenter study involving 464 cases of stage 3B and 4 NSCLC cases with a KRAS mutation, the mutation frequency was G12C (46%), G12V (20%), and G12D (10%), respectively. The PFS was statistically substantially longer in the platinum + taxane treatment group than in the platinum + pemetrexed or gemcitabine groups. In this study, the subgroup G12V is identified as the source of the difference. On the other hand, there was no difference in OS between chemotherapy regimens and KRAS mutation subgroups. In the study population, more than half of the patients in the platinum + taxane group received bevacizumab. The survival effect of adding bevacizumab to treatment has been demonstrated, and we think that the contribution to PFS could be attributable to bevacizumab.[12] The difference of our study is that there is a platinum + vinorelbine subgroup within the chemotherapy groups and we did not have a case involving the use of biological agents. Therefore, we believe the correlation between KRAS mutations and conventional chemotherapy combinations can be evaluated with more precision.

In a study examining 99 NSCLC cases, which is one of the first preclinical studies on drug sensitivity and tumor behavior of distinct KRAS mutations, it was revealed that the most prevalent mutations were G12C (39%), G12V (21.8%, G12D (15.5%). The three most frequently detected tumor clones were replicated to investigate the chemotherapy sensitivity. G12C-mutated tumor clones exhibited decreased sensitivity to cisplatin and increased sensitivity to taxane and pemetrexed. Moreover, the G12V clone was more resistant to pemetrexed and more sensitive to cisplatin.[5] This distribution is consistent with the frequency of mutations identified in our study population. Due to the inability to perform a submutation analysis on our cases, we could not comment on the chemotherapy response according to the KRAS subgroups.

Conclusion

In conclusion, there was no statistically significant difference in survival between platinum + taxane, platin + pemetrexed, platin + gemcitabine, and platin + vinorelbine that were used in the first-line chemotherapy of metastatic NSCLC cases with a KRAS mutation. Patient-specific characteristics, drug side effects, and patient preferences may be a determining factor in selecting chemotherapy for NSCLC cases with a KRAS mutation. The primary limitation of our study was our inability to analyze the effect of chemotherapy options based on the number of cases in the KRAS subgroups. Another limitation of our study is the limited number of patients treated with immunotherapy as first-line treatment. We believe our study will serve as a source for future research that will include more case groups and incorporate the combinations of chemotherapy and immunotherapy. Our study is the first to report the efficacy of chemotherapy in cases of KRAS mutant metastatic NSCLC in our country and at our institution.

Author Contributions

Mustafa Emre Duygulu was responsible for design, statistical analysis, and manuscript preparation. Data analysis was done by Atila Yildirim. Literature search was conducted by Eyyup Ayas. Data acquisition was done by Nese Alyildiz. Definition of intellectual content was provided by Sevdegul Aydin Mungan. Manuscript editing and manuscript review were done by Evren Fidan. All the authors read and approved the final version of the manuscript.

Patient Consent

None declared.

Funding

None declared.

Conflict of Interest

None declared

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Therapeutic Drug Monitoring of 5-Fluorouracil in Head and Neck Cancer Patients: An Interventional Pilot Study

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Ind J Med Paediatr Oncol 2024;45:134–141.

Abstract

Introduction 5-fluorouracil (5-FU) is a crucial agent in treating various types of cancer, particularly recurrent head and neck cancers (HNCs). According to prior studies, individuals who underwent therapeutic drug monitoring (TDM) based 5-FU dosage adjustments showed significantly higher response rates and experienced fewer adverse events compared with those who received the standard 5-FU administration. This study aims to enhance our understanding of the overall clinical outcomes in patients with recurrent HNCs who received 500 mg of 5-FU through a pharmacokinetic (PK) analysis.

Objectives Our objectives are to conduct TDM in selected HNC patients and observe individual PK responses, efficacy, tolerability, and drug toxicity.

Materials and Methods We enrolled a total of 12 patients with recurrent metastatic HNC, and all of them received a fixed dose of 500 mg with cisplatin in a 21-day cycle. During cycle II or III, we analyzed the blood concentrations and PK parameters of 5-FU using the liquid chromatography and mass spectrometry (LC–MS) technique. Notably, we calculated the Concentration maximum (C_{max}), time at which the concentration reaches maxiumum (T_{max}), Half life of the drug ($T_{1/2}$), and area under the curve (AUC) for the 500-mg dose of 5-FU, as the PK data for this particular dose were unavailable, making our study uniquely valuable for assessing efficacy and toxicity.

Results Within the study group, 83.33% obtained an average AUC range of 1,000 to 3,000 h/μg/mL. Out of this group, 41.66% showed a partial response, 33.33% experienced disease progression, and 25% remained stable during the therapy. One patient had an AUC below the expected value (832.21 h/μg/mL), while another had an overexposed AUC value (5726.87 h/μg/mL), resulting in a poor clinical outcome. After interpreting the results, suggestions for dosage adjustments were made to the clinician.

Conclusion From our interventional study, it is evident that at a flat dose of 500 mg, PK-based individual dosage regimens play a superior role in managing advanced cancer patients with minimal toxicities. This PK analysis showed us clarity on the outcomes of 5-FU at a 500-mg dose.

Keywords
- 5-fluorouracil
- therapeutic drug monitoring
- head and neck cancer
- dosage adjustments

article published online
October 25, 2023

DOI https://doi.org/10.1055/s-0043-1776294.
ISSN 0971-5851.

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

Introduction

An antimetabolite chemotherapeutic molecule, 5-fluorouracil (5-FU), has been used in the last six decades to treat multiple cancers, including gastrointestinal (GI), breast, ovarian, and head and neck cancers (HNCs). Head and neck squamous cell carcinoma (HNSCC) refers to the majority of head and neck malignancies, which are generated from the mucosal epithelium in the oral cavity, pharynx, and larynx. In most of these, quantifying the efficacy and establishing an individualized dose is still challenging for health care professionals and researchers. 5-FU is the primary component of combination chemotherapy in patients with metastatic HNCs. Like other anticancer drugs, 5-FU is administered by body surface area (BSA) based dosing in most practices.[1] Numerous studies have clinically proven suboptimal and poor outcomes in colorectal cancers (CRCs) treated with 5-FU in different regimens, such as folinic acid, fluorouracil and oxaliplatin chemotherapy drugs (FOLFOX)[2] and folinic acid, fluorouracil and irinotecan chemotherapy drugs (FOLFIRI).[3] But evaluating the efficacy of 5-FU in HNC has been stated in very few studies. Notably, stage III and IV locoregionally progressed tumors were found in roughly 60% of HNC patients.[4,5] Many patients had stage IV (stage IVA) tumors out of the two stages. The typical patient survival time for stage IV HNC patients with metastatic and locoregionally progressed HNC was approximately 10 months, whereas nonmetastatic stage IV HNCs were treatable.[6]

Therapeutic drug monitoring (TDM) is a part of clinical therapy in which a patient's drug level is continuously monitored for the concentration of a specific medicine to ensure that their dose regimens are working as effectively as possible.[7] TDM should be considered and recommended for improving the safety and efficacy of drugs with a narrow therapeutic index.[8]

The typical routine for administering 5-FU in concomitance with many anticancer drugs has been based on BSA, regardless of the regimen used.[9] Sadly, BSA dosing cannot fit the needs of different body types and leads to a wide range of 5-FU exposure. A study with 81 patients with metastatic CRC documented a lack of association between BSA and 5-FU.[10] An algorithm for 5-FU dosage adjustments was introduced by Wilhelm et al[11] in a study conducted in 14 HNC patients administered with cisplatin and a 5-day continuous infusion of 5-FU. Hillcoat et al reported a strong association between 5-FU plasma concentrations and tumor response in patients with GI malignancies in the 1970s.[9] All the patients got nitrosourea 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) 150 mg/m^2 on the first day, followed by a 5-day continuous infusion of 5-FU at a rate of 1,200 mg/m^2/d on days 1 to 5, delivered every 6 weeks. Measurements of plasma 5-FU concentrations revealed significant interpatient variability. Furthermore, the area under the curve (AUC) was found to be considerably larger in patients with either partial response (PR) or stable disease (SD) compared with those who did not have a tumor response. This first instance linked clinical data on 5-FU plasma exposure to clinical action. 5-FU is a highly saturable, narrow therapeutic index with a very short half-life of 8 to 20 minutes. This favors the trend to adopt a pharmacokinetic (PK) based dosing in cancer patients. Clinical investigations from the past few decades have demonstrated that individual 5-FU dose titration with PK monitoring results in a high and effective survival rate, a high positive response, and good tolerability in CRC and HNC patients.[12,13] The adverse event system of voluntary post-marketing reporting reviewed data from the U.S. Food and Drug Administration (FDA) suggested severe toxicities. Nausea, diarrhea, vomiting, mucositis, neutropenia, and palmar–plantar erythrodysesthesia (PPE) are examples of systemic Fluoropyrimidines (FP)-associated toxicities (FP-TOX).[14]

This pilot investigation enhances comprehension of disease progression, survival rate, and efficacy of chemotherapy in certain populations while providing updated information to clinicians on the safe and effective utilization of 5-FU. The main focus of this study is to examine the correlation between PK data and its impact on both treatment effectiveness and potential side effects when administering a constant 500-mg dose of 5-FU through intravenous infusion over 8 hours.

It is important to note that the actual treatment regimen involves a 2-day intravenous infusion of 5-FU + cisplatin, repeated every 21 days, with cisplatin playing a significant role in overall clinical outcomes. However, this evaluation specifically concentrates on observing the PK data of 5-FU at a flat dose of 500 mg.

Materials and Methods

Study Design

This is a prospective interventional study. Twelve patients diagnosed with advanced squamous cell carcinoma of the head and neck were studied in the Department of Clinical Research, Erode Cancer Centre, Tamil Nadu, India.

Inclusion and Exclusion Criteria

Recurrent HNC patients with normal renal, hepatic, and cardiac functions and good hematological status were included. Patients with renal failure or hepatic impairment, vulnerable populations (pediatrics and age above 75 years), obesity patients, medication histories, and those using drugs and alcohol that interfere with 5FU were excluded.

Primary and Secondary Objective

The primary objective was to perform TDM in selected HNC patients and to observe individual PK responses to the drug. The secondary objective is to assess the efficacy and tolerability based on PK values and monitor for toxicity and evaluate the overall clinical outcomes for the given dose.

Selection of Patients

Patients were selected based on the following criteria: (1) histologically confirmed and diagnosed with HNC; (2) recurrent metastatic disease; (3) no prior chemotherapy with 5-FU, and prescription of a 500-mg dose of 5-FU in cycles I and II; (4) WHO performance status of 0 to 2); and (5) tumor evaluations done with computed tomography (CT) scan,

magnetic resonance imaging (MRI), and biopsy. The sample size was determined based on the availability of patients during the study period.

Selected Patients and Sample Collection

Twelve recurrent metastatic HNC patients (8 males, 4 females) with a mean age of 55 years (range: 45–75 years) with histologically proven active stage III and IV cancers confirmed using TNM (*t*umor size, *n*ode involvement, and *m*etastasis status) staging and with a history of past radiotherapy for primary tumors were enrolled for the study. Tumors were localized in the oropharynx ($n=4$), tongue ($n=4$), buccal mucosa ($n=2$), and esophagus ($n=1$). The performance status of all the patients was ≤ 2. All the patients were given 5-FU and cisplatin throughout the study. Everyone was thoroughly evaluated based on a detailed history and HNC diagnostic and treatment criteria. We conducted relevant investigations, including positron emission tomography (PET) scans, CT and MRI, complete blood count (CBC), renal function test (RFT), liver function test (LFT), and electrocardiogram (ECG), frequently. A fine-needle aspiration cytology (FNAC) was done previously. A professional team of oncologists, pharmacists, nurses, and bioanalysts were involved throughout the study.

On day 0, patients were well hydrated with 5% dextrose (1 L), sodium chloride (NaCl; 6 g/L), and potassium chloride (KCl; 3 g/L). On day 1, 500 mL of dextrose was given with ondansetron (4 mg) and dexamethasone (8 mg). Later, 500 mg of 5-FU was mixed in 500 mL of normal saline (NS) and infused through an infusion pump at a rate of 1.41 mL/min (85 mL/h) for 6 hours. Blood samples were collected to estimate the drug concentration.[15] Then 20 to 60 mg of cisplatin in NS was given as a 5-hour infusion. On day 2, 1 g of 5-FU was given as a 12-hour infusion, followed by the same dose of cisplatin.

Blood Sampling and PK Analysis

The optimization of extraction trial for 5-FU was done with a bioanalytical team. As a result, the mobile phase, flow rate, column, and internal standards were fixed. Accordingly, six time points for sample collection were framed, which included predose (5 minutes before dosing) and 00.50, 01.00, 02.00, 04.00, and 08.00 hours on day 1. More than 80% of 5-FU elimination was done by the catabolic process of the rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD).[15,16] So the addition of DPD inhibitors is important for plasma separation. 5-FU has a short half-life of 10 to 15 minutes and would attain steady-state concentration in a few hours. In this, approximately 3 mL of venous blood was transferred to K2 EDTA (ethylenediaminetetraacetic acid) tubes and centrifuged in the laboratory immediately at 4,000 rpm for 10 minutes. The supernatant portion after precipitation was then transferred to respective aliquots and stored at –70°C until analyzed. All the samples were sent for PK analysis using the liquid chromatography and mass spectrometry (LC-MS) technique under controlled conditions.

Pharmacokinetic Investigation and Assessment

PK investigations were done. The AUC at 0 to 8 hours was calculated by the trapezoidal rule. Along with that, C_{max}, T_{max}, concentration of drug at last (Clast), time where concentration of drug is last (Tlast), volume of distribution (Vd), Concentration at steady state (Css), $T_{1/2}$, elimination rate constant (Ke), and clearance of drug (CL) for the flat dose of 500 mg for all the patients were recorded. For each patient, the 5-FU exposure based on AUC was compared with the average. The RECIST (response evaluation criteria in solid tumors) criteria were assessed for overall PK response.

Statistical Analysis

Descriptive statistics were deemed necessary to observe the percentages, mean standard deviation (SD) range, and median range for all patient demographic characteristics. The regression statistics were used for a comparison of the PK parameters. The level of significance was set at $p=0.05$. The software PK = SOLVER was used for most of the analyses (version 2.0; Microsoft Excel USA Software, Inc).

Ethics

This study was approved by the institutional ethical committee before the study began (approval reference number: SVCP/IEC/SEP/2021/09). All the procedures followed were under the ethical standards of the responsible committee on human experimentation and in compliance with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all the patients for inclusion in the present study.

Results

Patient Characteristics

The study performed TDM of 5-FU in 12 patients, comprising 8 males (66.6%) and 4 (66.6%) females, mostly falling under normal body mass index (BMI) and mean age of 45 to 55 (92.7%) and receiving 500 mg of 5-FU on day 1. In all, six (50%) and seven (58.3%) patients had no past medical and medication history, respectively. Of these, 5 (41.6%) were smokers and alcoholics in the past. Four of 12 (33.3%) patients had oropharyngeal cancer, and another 4 (33.3%) had tongue cancer. Seven patients (58%) had multiple metastatic lymph nodes. Toxicity was mild. Nausea experienced by 11 (91.66%) patients and there was grade 1 stomatitis in 1 (8.3%) patient. All the patients were coded between Therapeutic drug monitoring of 5-Fluorouracil of first patient (TDM5FU001) and TDM5FU012. Their basic characteristics of the patients are summarized in ►**Table 1**.

Pharmacokinetic Parameters

Overall, individual PK response from the selected population was appreciable (►**Table 2**). A considerable difference in disease progression with better therapeutic tolerance was noted with the flat dose of 500 mg of 5-FU. The target was not achieved by only two patients (►**Figs. 1** and **2**). Laboratory investigations were done pre- and postdosing and the corresponding observations for toxicity were done. Postdosing,

Table 1 Patient demographics

Patient characters		No. of patients (maximum, $n = 12$)
Gender	Male	8 (66.6%)
	Female	4 (33.3%)
Age (y)	45–55	7 (58.3%)
	56–65	4 (33.3%)
	66–75	1 (8.3%)
WHO performance status	0	3
	1	9
	2	0
Social History	Smoker	1 (8.3%)
	Alcoholic	1 (8.3%)
	Smoker and alcoholic	5 (41.6%)
	Betel nut	2 (16.6%)
	Smoking and betel nut	2 (16.5%)
	No social history	1 (8.3%)
BMI	Underweight	3 (25%)
	Normal	2 (16.6%)
	Overweight	7 (58.3%)
Diagnosis	Oropharyngeal cancer	4 (33.3%)
	Tongue cancer	4 (33.3%)
	Buccal mucosa cancer	2 (16.66%)
	Tonsil and esophageal cancer	2 (16.6%)

Abbreviation: BMI, body mass index.

Table 2 Observed pharmacokinetic (PK) values

PK parameters	Observed range	Deviated samples	
		Therapeutic drug monitoring of 5-Fluorouracil of fifth patient (TDM5FU005)	Therapeutic drug monitoring of 5-Fluorouracil in sixth patient (TDM5FU006)
Area under the curve	1,000–3,000 h/μg/mL	5.726.878	832.217
C_{max}	500–1,000 ng/mL	1819.322	335.056
T_{max}	00.50–01.00 h	02.00 h	00.50 h
Clearance	0.100–0.300 L/h	0.086	0.5536

hematological parameters (hemoglobin, RBC, platelet, lymphocytes, polymorphs, etc.) showed reduced count to predosing blood count. There was an increase in the blood glucose range compared to the range before intervention. Nausea was predominantly seen in all samples and stomatitis with grade 1 was observed in one patient (►**Fig. 3**).

Comparison of Pharmacokinetics

Deviated samples: The AUC and tumor reduction were plotted in a normal probability plot using regression statistics (►**Fig. 4**). The *R*-value from the correlation using regression statistics was 0.16, that is, the *R*-value is progressing toward a positive factor. In the case of a large sample population, the relation between AUC and tumor size reduction will be clearer.

Interpretation of the R value is as follows:

- 0: relation cannot be predicted.
- +1: positive relation between variables.
- –1: negative relation between variables.

The underdosed sample showed reduced C_{max}, T_{max}, and AUC and increased clearance, while the overdosed sample showed increased C_{max}, T_{max}, and AUC and reduced clearance. We have attained the expected target in 10 samples (84.4%).

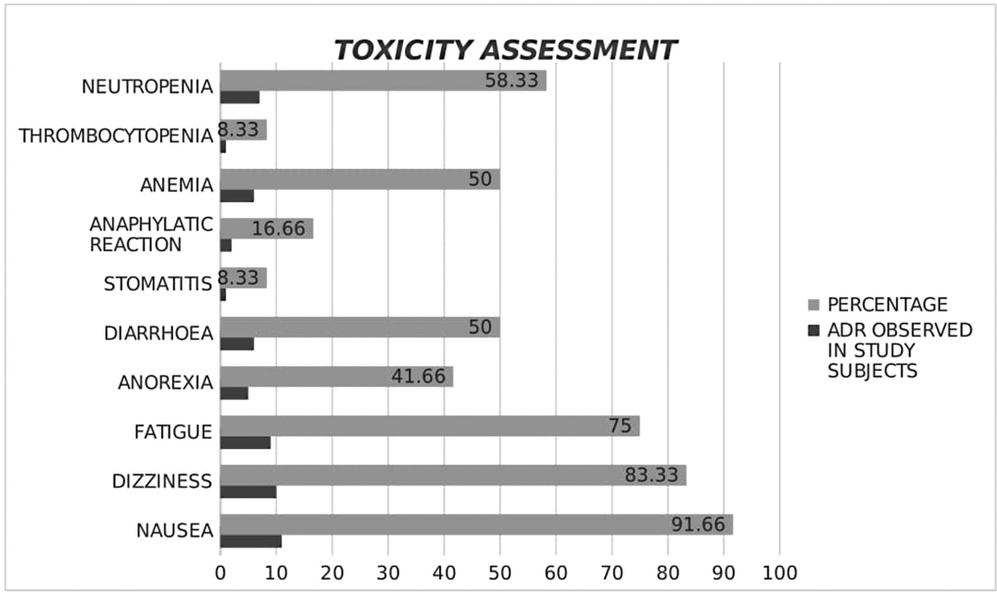

Fig. 1 Toxicity assessment of study population. Toxicity changes occurred in patient while on 5-fluorouracil treatment. Nausea and dizziness were predominant. ADR, adverse drug reaction.

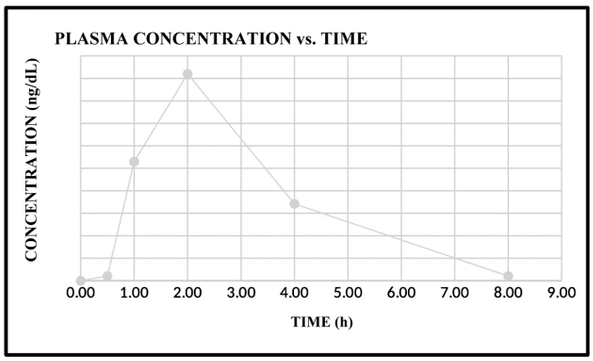

Fig. 2 Concentration versus time graph. A 64-year-old female patient of was on 5-fluorouracil treatment. Samples were collected and the concentration versus time graph was plotted and displayed. The graph shows the area under the curve concentration is increased, indicating the patient requires low dose.

$p = 0.615$ ($p > 0.05$): The p value calculated for the AUC range and intercept was greater than 0.05. So the AUC range and the outcome were not statistically significant. The result shows nonsignificance of the p value due to small sample size and disease progression. The results indicated that one (8.3%) patient was underdosed and showed decreased maximum concentration (C_{max}) and below the AUC range. One (8.3%) patient showed increased maximum concentration (C_{max}) and AUC range. Ten (84.4%) patients were under an optimum range.

Response Rate

The response evaluation was represented using the RECIST criteria for 12 subjects. PR was observed in five (41.66%) patients, disease progression in four (33.33%) patients, and stable response in three (25%) patients. No complete responses were observed.

Discussion

In advanced HNC, the main goal of chemotherapy is to relieve symptoms. Slightest increase in their response rate can improve their quality of life. In general, when administered as first-line therapy, combination chemotherapy has response rates that are 10 to 15% greater than those of single-agent chemotherapy (15–40%).[17,18] Only a tiny proportion of patients with stage III or IV locoregionally progressed HNCs are treated by radiation or surgery. Concurrent radiation and chemotherapy treatment may yield better outcomes in terms of lifespan and disease-free life expectancies.[19]

Numerous studies have shown that an individual's response to chemotherapy is significantly influenced by the PK heterogeneity of 5-FU in them.[2,20] Age-related changes in physiology and biological traits may affect the PK of medicines, alter plasma concentrations, and ultimately influence the acceptability and efficacy of chemotherapy. The variability in the steady-state concentration may also be due to changes in the infusion pump or drug collection. When therapy is based on BSA or a flat dose, the clearance of 5-FU exhibits significant intersubject variability that is not diminished. The BSA-based dose was personalized for individual patient dosing of chemotherapy drugs.[21] Another major point is that the drug is unstable in blood and plasma at room temperature, while the catabolism of 5-FU is handled by the DPD enzyme.[11,22–24] Many studies have been conducted to evaluate the efficacy of a dose-modifying algorithm and demonstrate the advantages of a 5-FU PK-guided dosing pattern for reducing toxicity and enhancing therapeutic outcomes, although BSA is an accepted method for determining 5-FU dosage. TDM and adjustment of the

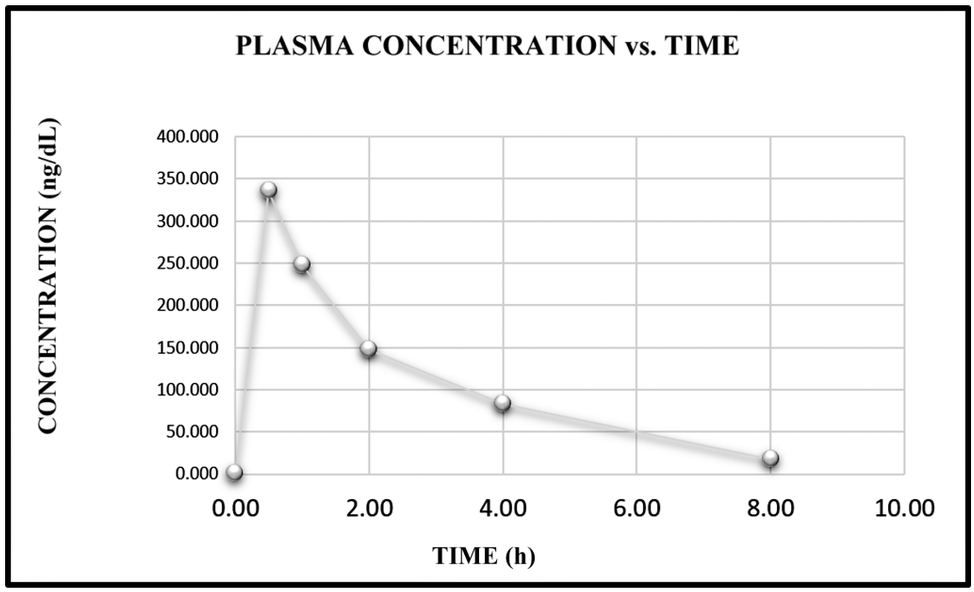

Fig. 3 Concentration versus time graph. A 53-year-old male patient was on 5-fluorouracil treatment. Samples were collected and the concentration versus time graph was plotted and displayed.

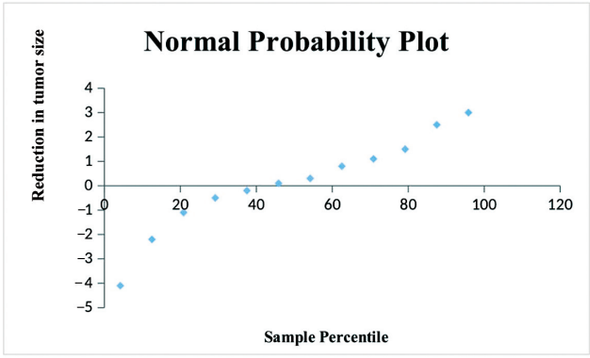

Fig. 4 The normal probability by regression statistics. The plot shows the regression graph of area under the curve concentration and tumor size reduction. The regression value is 0.16. It shows that the plot is moving toward a positive correlation.

5-FU concentration significantly improved the efficacy of chemotherapy.[25]

In our study, we chose 12 recurrent HNC patients diagnosed with tongue cancer (4), oropharyngeal cancer (4), buccal mucosa cancer (2), tonsil cancer (1), and esophageal cancer (1) in palliative care who underwent combination chemotherapy of cisplatin and 5-FU. The age range was between 45 and 75 years. We found that increasing dosage in underdosed individuals may assist in minimizing toxicities and complaints from the present cycle to subsequent cycles in progressing malignancies. At the initial cycle, a flat 5-FU dose of 500 mg was administered. No difference in terms of the 5-FU combination was observed. However, all the patients received 500 mg of 5-FU + cisplatin on day 1 and 1,000 mg of 5-FU + cisplatin on day 2 as a cumulative total regimen for a 21-day cycle. As a reminder, for this study, individual dose adjustment was based on systemic exposure measured from TDM. An average AUC range of 1,000 to 3,000 h/µg/mL was obtained in 83.33% of the group, with two exceptions. One was under the expected AUC (832.21 h/µg/mL) and one had an overexposed AUC value (5,726.87 h/µg/mL). Both cases showed wide variability in PK parameters.

This result led to an important variability in 5-FU steady-state concentrations, ranging from 130 to 541 mg/L for an identical total dose of 500 mg. The Css in two cases (16.66%) showed a significant change in their AUC and was subjected to poor clinical outcomes (i.e., disease progression). Similarly, the PK parameters of all the patients were interpreted according to the clinical outcome. PR was observed in 41.66% of the patients, disease progression in 33.33% patients, and SD in 25% patients. Suggestions for dosage adjustments were made to the clinician after interpreting the results. In Saam et al,[2] the 5-FU AUC was recorded for 4 cycles in 64 CRC patients prescribed with any regimen in which 5-FU was administered throughout 44 to 48 hours. The first measurement indicated that 68% of patients were underexposed, 13% were under the therapeutic range, and 19% had a superior AUC target level. A clinical trial conducted by Macaire et al focused on assessing the benefit-to-risk ratio in elderly individuals. The study investigated the relationship between 5FU exposure and toxicity while also comparing the effectiveness of 5FU therapeutic drug monitoring (TDM). The drug was monitored on cycle 1, and blood samples were drawn. Further dosage adjustments were made. Results showed a percentage difference between older and younger patients. The AUC of 5-FU at cycle 2 was 64% in older and 68% in younger patients. The toxicity level decreased compared with the first cycle after dose adjustment. Their results demonstrate that the vast majority of patients are not in the expected therapeutic range after receiving a standard 5-FU BSA-based dose. The high interindividual variability after dose adaptation testifies to a very limited interest in 5-FU

BSA-based dosing. Upon 5-FU PK-guided dose adjustment in subsequent cycles, a significant decrease in this variability was observed.[23] The clinical outcome was evaluated through imaging studies at the end of chemotherapy, and the interpretation revealed some publications describing increased rates of nausea, diarrhea, stomatitis, leukopenia, or neutropenia.[11,23] In our investigation, after a standard flat dose of 500 mg, the following common toxicity symptoms were observed: nausea (91.66%), vomiting (25%), dizziness (83.33%), fatigue (75%), anorexia (41.66), diarrhea (50%) and moderate stomatitis (8.33%), anaphylactic reaction (16.66%), anemia (50%), thrombocytopenia (8.33%), and neutropenia (58.33%). However, both toxicity and clinical outcome depend on the activity of 5-FU given with cisplatin as a combination therapy. We observed that grade III and IV toxicities were associated with a higher AUC range than grade I and II toxicities. Conversely, almost twice as many toxicities were observed among overexposed patients compared to patients who were underexposed or well exposed.

The results show that the flat dose gives a significant positive response in most cases along with lower toxicity. All 12 recurrent HNC patients in the study underwent TDM, and all the PK parameters were assessed. The target AUC was obtained in approximately 83.33 %. Dose alterations were made for the under- and over-exposed patients. Toxicities were mild and moderate with manageable conditions. Out of 12 subjects, 41.66 % showed PR, 33.33 % showed disease progression, and 25% were stable.

The main limitations of our study are the small sample size and the short study time. A multi-centered study with a large sample size might give more detailed and confirmatory reports of the relationship between dose and clinical response of 5-FU at a flat dose.

Future studies should come up with preemptive pharmacogenetic testing that confidently enhances 5-FU exposure in a significant number of patients. Despite the abundance of positive shreds of evidence supporting the 5-FU TDM, the clinical routine of PK tests has not been widely established. To fully enter the era of precision medicine, a model framework incorporating the PK and pharmacodynamics of 5-FU will be necessary. The use of model applications may also help clinicians determine the appropriate dose before beginning chemotherapy.

Conclusion

From our interventional study, it is evident that at a flat dose of 500 mg, PK-based individual dosage regimens play a superior role in managing advanced cancer patients with minimal toxicity. The study population involving 12 recurrent HNC patients underwent TDM, and all the PK parameters were assessed. The target AUC was obtained in approximately 83.33% of patients. Two patients who deviated from the expected therapeutic window were considered for dosage adjustments. The dose was increased to 750 mg + 1 g in patient 6 in the next cycle and patient 5 was prescribed 350 mg + 750 mg by the clinician. PR was observed in 41.66% patients, disease progression in 33.33%, and SD in 25% patients. This PK analysis showed clarity on the outcomes of 5-FU at a 500-mg dose.

A small sample size and a non-PK-based dosage regimen before TDM may be the cause of the nonsignificance of our results. However, the significance of a sample size of 12 showed positive progress with a regression value of 0.16. Increasing the sample size to more than 30 with extended follow-up can have a greater impact by establishing a detailed PK response for 500 mg of 5-FU. This single-center pilot study gives hope for managing advanced HNC patients with flat doses for better tolerability while reducing toxicity. Its precise role in the management of HNC remains to be determined at a larger scale.

Author Contributions

N.K.B, N.D., and S.D.B. were responsible for the concept and design of the study, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and literature search. Critical revision of the manuscript for important intellectual content was done by K.V. and P.S.N. They also provided administrative, technical, or logistic support. PSN contributed to design the study protocol and supervised the study.

Statement

The manuscript has been read and approved by all the authors, and the requirements for authorship have been met.

Patient Consent

The consent from the patient has been taken to participate on this study.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgments

We express our sincere thanks to our honorable chairman of Vivekanandha Educational Institutions for allowing us to carry out this work and for providing us with all the facilities for the study. We are thankful to our Principal, Swamy Vivekanandha College of Pharmacy (SVCP) and the Department of Pharmacy Practice, SVCP for their support throughout the study. We thank all the physicians and nurses at the Erode Cancer Centre for their kind support. Our sincere thanks also go to INNOSPECS BIOANALYTICAL LABORATORY for the pharmacokinetic analysis.

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A Survey on Unmet Need for Uniform Next-Generation Sequencing Reporting in India

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Ind J Med Paediatr Oncol 2024;45:142–146.

Abstract

Introduction: Next-generation sequencing (NGS) has paved the way for precision oncology in oncology clinics today. With rapidly advancing therapeutics, it is becoming increasingly important to obtain information about the molecular milieu of a patient's tumor. However, reporting and interpreting of NGS is fraught with complexity and variability. To understand the questions surrounding NGS reporting in India, we conducted a survey.

Objectives: The aim of this study was to assess the gaps in NGS reporting and interpretation in Indian medical oncology clinics.

Materials and Methods: An anonymized 10-question survey-based study among Indian medical oncologists through Google forms was conducted between October 4 and 8, 2022.

Results: The sample size was $n = 58$. Seventy-one percent felt there was heterogeneity in NGS reporting, 72% were unaware of NGS reporting guidelines, and 62% did not feel the need for a molecular scientist assist in NGS interpretation. Almost all (98%) felt there was a need for uniform NGS reporting as well as an Indian NGS repository and data-sharing system (93%).

Conclusion: Our survey highlights the need for a uniform national guideline concerning NGS reporting.

Keywords
- next-generation sequencing
- uniform reporting
- guidelines

Introduction

Precision medicine or personalized medicine uses molecular diagnostics to guide diagnosis and prognosis and to offer individualized therapy based on the presence of somatic and/or germline genetic alterations.[1] Next-generation sequencing (NGS) allows for multiple parallel sequencing of the whole genome, exome, or a targeted gene panel in a short time span. This has propelled the use of precision medicine in oncology clinics today with an unprecedented speed.[2] The relevance of NGS in the management of malignancy continues to grow with the advent of tissue-agnostic therapy.[3] However, there are multiple limitations to the purported benefits of utilizing NGS in clinical practice—difficulty in the interpretation of complex reports, lack of validation, sensitivity and specificity of reported results, relevance to variants detected, continuously evolving data, identifying fusions and indels, and the high cost of NGS. Tumor heterogeneity and adequate tissue material remain an added challenge. Once a proven targetable mutation is detected, access to costly drug

article published online
July 5, 2023

DOI https://doi.org/10.1055/s-0043-1770936.
ISSN 0971-5851.

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

and lack of clinical trials in India create an unnecessary, uncomfortable situation for the patients and their doctors.[4,5]

To counteract these limitations, organizations have developed guidelines, from correct processing of the tissue samples to methods of validation and establishing controls to proper ways to compile an NGS report so that it is easier to apply in clinical settings.[6–9] To understand the real-world challenges medical oncologists face in the country, we planned a short survey.

Materials and Methods

We conducted an anonymized survey-based study among Indian medical oncologists. Practicing medical oncologists were questioned regarding their views on NGS reporting and its applicability in day-to-day practice. The survey consisted of 10 questions, with yes/no ± maybe as options for 7 questions; 1 was on a Likert format of graded responses, and 2 were open-ended. Details of the survey are depicted in ►**Table 1**.

This survey was conducted from October 4 to 8, 2022. The survey was circulated through social media apps and email. Google forms platform was used. All data were anonymized and the study was performed in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later amendments.

Outcome of the study: to identify the pitfalls in NGS reporting and interpretation in routine practice of medical oncology in India through open- and close-ended questions.

Inclusion criteria and exclusion criteria: any medical oncologist practicing in India who was willing to fill the questionnaire was included in the study, irrespective of gender, locality, and type of practice or years of experience.

Statistical analysis data were collected and analyzed using Microsoft Excel for Mac, version 16.43 (Redmond, WA, United States) and Google forms platform. Descriptive statistics were used to assimilate and represent data, and frequencies, percentages, means, and standard deviations were used where appropriate.

Table 1 Survey questionnaire

No.	Questions	Answers
Q1	Are you a medical oncologist?	Yes No
Q2	How often do you feel that there is heterogeneity in NGS reporting in India or elsewhere?	Often Rarely Not relevant to me
Q3	Do you feel that for every NGS report, you need help from a molecular scientist?	Yes No
Q4	Have you ever come across NGS reporting guidelines?	Yes No
Q5	If yes, please mention the guidelines and how many molecular laboratories follow the guidelines?	Long answer
Q6	Do you feel there is a need for uniform NGS reporting?	Yes No
Q7	In how many cases, do you feel helpless when NGS reports give options of unavailable therapy in India?	100% 75–100% 25–75% <25%
Q8	Do you feel that there is a need for uniformity, accountability, and quality assurance of NGS procedure and reporting in India?	Yes No
Q9	Do you feel that India should have a NGS repository and data-sharing system?	Yes No Maybe
Q10	What parameters do you want in NGS reporting?	Open question

Abbreviation: NGS, next-generation sequencing.

Result

Fifty-eight medical oncologists responded to the survey. The responders felt that there was heterogeneity in NGS reporting 71% of the time (►**Fig. 1**). Seventy-two percent of medical oncologists were unaware of any NGS reporting guidelines; the remaining were aware of some guidelines, such as European Society of Medical Oncology (ESMO)-ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) guidelines, College of American Pathologists-Clinical Laboratory Improvements Advisory Committee (CAP-CLIAC) guidelines, American College of Medical Genetics and Genomics and the Association for Molecular Pathology(-ACMG/AMP), and AMP-American Society of Clinical Oncology (ASCO)-CAP. Barring one person, most of them were unaware of whether the labs in India were adhering to any guidelines.

While the majority (62%) did not feel the need for a molecular scientist to interpret an NGS report, overwhelmingly, 98% felt an unfulfilled need for uniform NGS reporting. When asked if there was a "need for uniformity, accountability and quality assurance of NGS procedure and reporting in India," 97% responded in the affirmative. Similarly, almost all (93%) agreed that India should have an NGS repository and data-sharing system (►**Fig. 2**).

About 40% felt helpless when NGS reports suggest a therapy inaccessible to their patients (►**Fig. 1**).

The final question asked the participants what parameters they would like to include in NGS reporting. The responses included suggestions such as a quality check, an explicit depiction of the method used, depth of reading, the number of reads, number of genes covered, tumor content, variant allele frequency and variants of unknown significance, allele frequency, actionable mutations and available drugs as well as incidence and available data of uncommon mutations, the tier of the mutations, fusions and whether RNA is used for checking them, tumor mutational burden with microsatellite instability, both RNA and DNA sequencing, mutations with prognostic implications, lab accreditation details, the platform used, haplotype map utilization for limits of detection, whether it is validated and compared to standard, and reporting in the context of the primary tumor diagnosis.

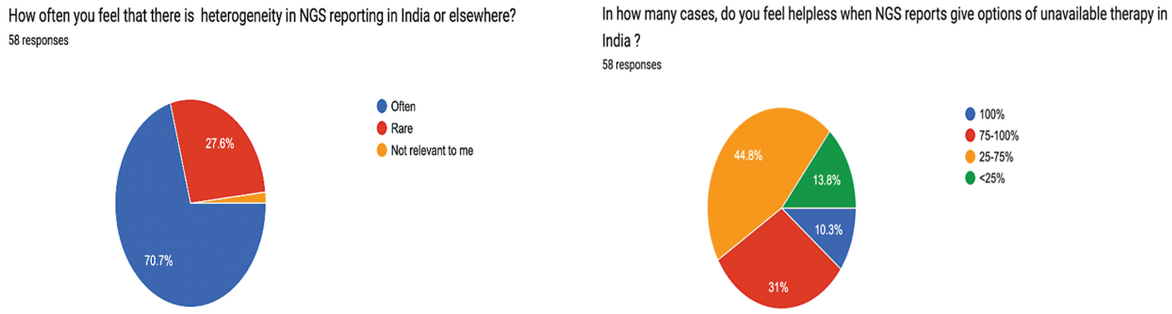

Fig. 1 Pie chart showing the distributions of answers to Questions 2 and 7.

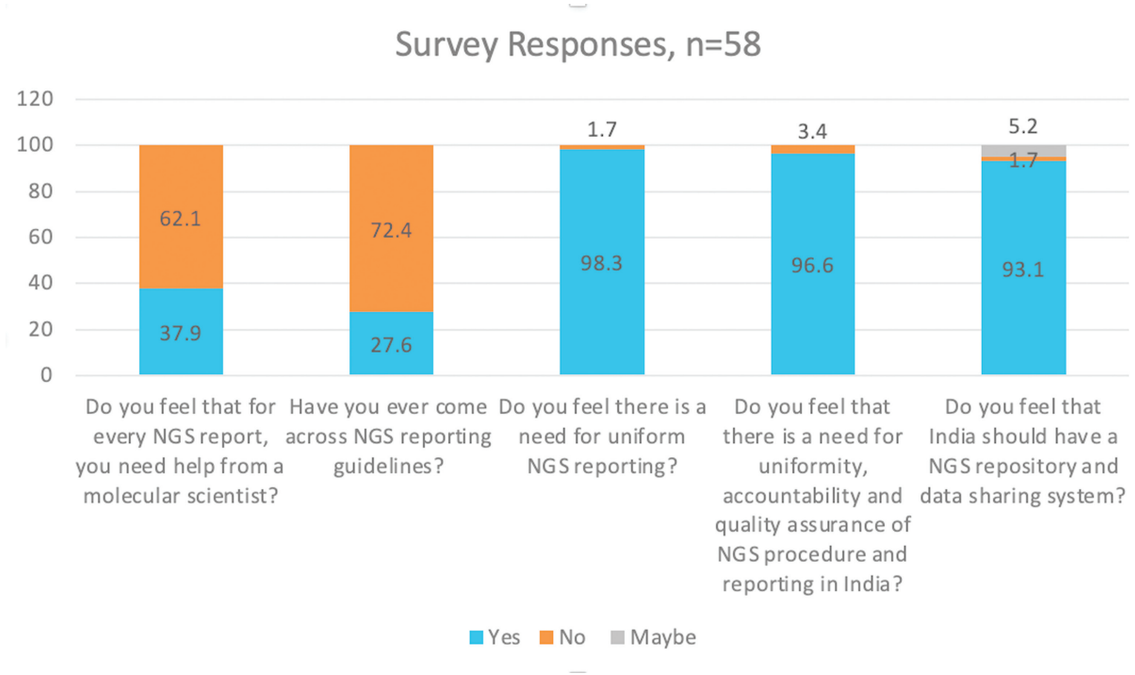

Fig. 2 Bar diagram depicting answers to survey questions 3, 4, 6, 8, and 9.

Incorporation of the option of a certified genetic counsellor for both pre- and posttest counselling was also suggested.

Discussion

There is a pressing requirement for standardization of NGS reporting, validation of existing tests against a gold standard, and formalizing a set of recommendations per tumor site. Furthermore, the interpretation of a positive result, its applicability to a particular patient, and the ramifications of cost are essential concerns.

The promise of precision medicine comes from specific therapies tailored to the genomic landscape of a patient's tumor, the growing successful avenues of tumor-agnostic therapy,[3,10] the favorable toxicity and better outcome profile of targeted therapy that act on oncogenic drivers,[11] and the indubitable success of immunotherapy.[12] However, this arena is clouded with uncertainty and limitations.[13] Even among oncologists using NGS routinely, the confidence to correctly interpret reports is low to moderate.[14] This partly stems from the continuously evolving body of literature surrounding genetic alterations—what is a "variant of unknown significance" today may be a targetable mutation tomorrow. In addition, many abnormalities identified in tumor DNA are often also seen in normal cells, which do not progress to a malignant state.[15] Furthermore, the detection of fusions and genetic aberrations affecting introns are complex and, many times, require additional RNA-based NGS.

A sizeable self-reported survey in 2018 by Freedman et al revealed that 75% of oncologists use NGS in routine clinical practice, with younger age of the physician, setting of an academic center, access to genomic training, and molecular-based tumor boards predicting greater usage. Compared with our study, in which 62% did not feel the need for a molecular scientist to interpret the NGS report, 49% in the study by Freedman et al had no difficulty in comprehending NGS reports.[13]

An important aspect of the applicability of NGS reporting is the financial burden of testing and the action that can be taken if a positive result is obtained. The ESMO/ESCAT guidelines address this issue. They have recommended NGS testing in only certain malignancies, such as lung adenocarcinoma, cholangiocarcinoma, and prostate cancer, where testing by NGS is more financially sound than other methods of molecular testing. On the other hand, for colon cancer, NGS is suggested as an alternative to polymerase chain reaction testing. The ESMO guidelines further have divided the possible genetic alterations into priority levels, labelled as tiers, which help guide management.[9,16]

In contrast to most developing countries, India is one of the few nations contributing to genomic research and development significantly.[17] The unique health care model of India with the availability of approved generic drugs,[18] both government and privatized health care, emerging indigenous techniques of NGS, and the rapidly developing science of precision medicine all culminate in a strong message for the need for standardized NGS reporting guidelines, a sentiment shared by 98% of our responders. Most of our participants felt the need for an Indian repository (93%). There is a need for a repository consisting of Indian variants of known and unknown targets to identify and address ethnic differences, as large international databases such as The Cancer Genome Atlas (TCGA) have largely underrepresented the Asian and African populations.[19,20]

Our study has certain limitations of small sample size and lack of demographic data and predictive factors impacting results, being an anonymized questionnaire. However, it is the first survey of its kind to be conducted in our country that have taken the questions of importance to the community and academic oncologist alike.

Conclusion

To conclude, our study has highlighted the imminent need of a national-level protocol to be established for the clinical application of genomic data to optimize patient care.

Author Contribution:
Neha Pathak: intellectual content, literature search, manuscript preparation, manuscript writing, and manuscript review.
Anu R. I.: concept, design, intellectual content, data acquisition, data analysis, and statistical analysis.
Padmaj Kulkarni: design, manuscript editing, and manuscript review.
Amol Patel: concept, design, intellectual content, data acquisition, data analysis, statistical analysis, literature search, and manuscript review.

Source of Funding
Nil.
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.

Conflict of Interest
None declared.

Acknowledgment
We thank all medical oncologists who participated in the survey.

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Hepatic Dysfunction during Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma and Its Effects on Subsequent Therapy and Outcome

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Ind J Med Paediatr Oncol 2024;45:147–152.

Abstract

Introduction The overall survival rate for childhood acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) has shown tremendous growth in the recent years. Hepatic dysfunction is one of the complications seen during therapy and can add to the underlying morbidity of the disease, delay in chemotherapy, modification of drugs, and rarely fulminant hepatic failure.

Objective This article aims to find out the prevalence of hepatic dysfunction during induction chemotherapy for ALL and LBL.

Materials and Methods This was a retrospective study, where the data of all children between 1 and 18 years of age with ALL and LBL treated at our center as per the UK-ALL 2003 protocol between December 2013 and December 2021 have been included from the medical records. Hepatic dysfunction was defined as grade 3 and 4 alanine transaminase (ALT) and aspartate transaminase (AST) levels as per Common Terminology Criteria for Adverse Events v5.0 and hyperbilirubinemia as $\geq$ 1.4 mg/dL as the chemotherapy modification begins at this cutoff. Data from children with hepatic dysfunction was compared with those without hepatic dysfunction using chi-squared test and Student's *t*-tests. Those variables with a *p*-value of < 0.2 were analyzed with multivariate regression analysis. Kaplan–Meier survival estimates were used to calculate the event-free survival (EFS).

Results A total of 142 children were included in the study. Thirty-one (21.8%) children developed hepatic dysfunction, 14 (9.9%) of them with ALT/AST elevation and 27 (19%) with bilirubin elevation. Weight (mean 25 ± 13.5, p 0.01), body surface area (mean 0.87 ± 0.29, p 0.02), and National Cancer Institute high risk (p 0.005) were associated with hepatic dysfunction in univariate analysis but none of them were significant in multivariate regression analysis. Treatment modification was required in 14/31 children with hepatic dysfunction. Death in induction was more among children with hepatic dysfunction ($p < 0.001$). There was no significant impact on minimal

Keywords
- acute lymphoblastic leukemia
- lymphoblastic lymphoma
- hyperbilirubinemia
- chemotherapy

article published online
February 27, 2024

DOI https://doi.org/10.1055/s-0043-1774780.
ISSN 0971-5851.

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

residual disease outcomes. Five-year EFS (death or relapse) was 59.93 ± 9% in children with hepatic dysfunction as opposed to 72 ± 5.0% in those without hepatic dysfunction (95% confidence interval, $p = 0.07$).

Conclusion One in five children with ALL and LBL on induction therapy developed hepatic dysfunction. Almost half of those with hepatic dysfunction required chemotherapy modifications.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer affecting children, accounting for 30% of all malignancies.[1] The overall survival rate for childhood ALL has shown tremendous growth in the past two decades due to the introduction of evidence-based risk-stratified protocols and improved supportive care.[2,3] Lymphoblastic lymphoma (LBL) is a rare aggressive neoplasm developing from B/T cell precursor cells predominantly in children and young adults. International standards currently recommend treatment as per intensive pediatric lymphoblastic leukemia protocols with an improved survival rate of almost 90% in children.[4] Remission induction is a major block of chemotherapy, and several complications are known to occur during this phase—febrile neutropenia, sepsis, bleeding, anemia, gastrointestinal disturbances, hepatic dysfunction, pancreatitis, venous thrombosis, etc.[5] Hepatic dysfunction could be due to leukemic infiltrates in the liver, nonalcoholic steatohepatitis, sepsis, hepatotropic viral infections, therapy-related toxicity seen due to asparaginase, rarely hyperinflammatory syndromes like hemophagocytic lymphohistiocytosis (HLH), and indirect hyperbilirubinemia due to underlying genetic syndromes like Gilbert's syndrome.[6] Hepatic dysfunction can contribute to morbidity by adding on to the underlying disease, delaying chemotherapy, dose modifications of chemotherapeutic agents, and rarely can cause mortality due to fulminant hepatic failure. This study was intended to find out the prevalence of hepatic dysfunction during induction therapy and its risk factors and effects on therapy and outcome.

Materials and Methods

This was a retrospective data analysis of all the children with ALL and LBL admitted to our center between December 2013 and December 2021. Children between 1 and 18 years of age with ALL or B/T cell LBL who underwent induction therapy at our center as per The UK-ALL 2003 protocol, which is the standard of care at our center, were included in the study.[7,8] Those children who were started on different chemotherapy protocols were excluded.

Remission Induction Therapy

Children with B-ALL and National Cancer Institute (NCI) standard risk (i.e., age 1–10 years with leucocyte count less than 50,000 cells/mm^3) were given three-drug induction (regimen A) with dexamethasone, vincristine, and asparaginase. Children with B-ALL and NCI high risk (age > 10 years and/or leucocyte count more than 50,000 cells/mm^3) and all the children with T-ALL and B/T LBL were given four-drug induction (regimen B) with dexamethasone, vincristine, daunorubicin, and asparaginase. Intrathecal methotrexate therapy was given as per the protocol. All the children on regimen B chemotherapy received oral antifungal prophylaxis with voriconazole (9 mg/kg/dose, twice a day) with temporary interruptions during vincristine administration. All the children were on oral cotrimoxazole 2 days a week as anti-*Pneumocystis jirovecii* prophylaxis. The duration of induction therapy lasted for 5 weeks.[7,8]

Data Collection

The patient case notes from the medical records department, hospital laboratory reports track- care system, and oncology database were reviewed. The demographic data like age and sex; disease-related data like B/T cell disease, central nervous system disease status, and risk stratification (NCI standard risk/high); blood tests like white blood cell counts, lactate dehydrogenase (LDH) levels, and uric acid levels at presentation, viral serology (human immunodeficiency virus and hepatitis B for all patients), and liver function tests throughout the induction; treatment-related data like the type of asparaginase used, drug modifications—delay or dose reductions if any; induction outcomes (end of induction minimal residual disease [MRD]); number of deaths; and relapse and survival data (from beginning of therapy to last follow-up/death/relapse) were collected in a standard pro forma.

Definition of Hepatic Dysfunction

Though not all hepatic dysfunctions were due to drug toxicity, we used Common Terminology Criteria for Adverse Events (CTCAE) cutoffs to define hepatic dysfunction to maintain uniformity.[9] Hepatic dysfunction was defined as grade 3 (> 5 to 20× the upper limit of normal [ULN]) and grade 4 (> 20× the ULN). Alanine transaminase (ALT) and aspartate transaminase (AST) levels as per CTCAE v5.0 and hyperbilirubinemia as ≥ 1.4 mg/dL (CTCAE mentions grade 2 as 1.5–3× the ULN, grade 3 as 3–10× the ULN, grade 4 as >10× the ULN) as the chemotherapy modifications begin at this cutoff as per the UK-ALL 2003 protocol.[7] Liver function tests were done in all the patients at presentation and as required throughout the induction—before administering vincristine, clinical icterus, or septicemia.

Table 1 Distribution of patients between hepatic dysfunction and no hepatic dysfunction and multivariate regression analysis

Parameter	Hepatic dysfunction, yes		Hepatic dysfunction, no		RR (95% CI)	Adjusted *p*-value
	n	%	*n*	%		
Age groups (y)						
Up to 10	22	19.0	94	81.0	1	0.80
> 10	9	34.6	17	65.4	0.89 (0.33–2.4)	
Diagnosis						
B cell ALL	22	18.6	96	81.4	0.83 (0.39–1.74)	0.61
T cell ALL	7	35.0	13	65.0	1	
B lymphoblastic lymphoma	1	50.0	1	50.0	1.6 (0.47–5.3)	0.46
T Lymphoblastic lymphoma	1	50.0	1	50.0	1.28 (0.33–5.1)	0.72
NCI risk						
Standard risk	9	12.3	64	87.8	1	0.11
High risk	22	31.9	47	68.1	2.0 (0.85–4.9)	
BSA					1.9 (0.39–9.6)	0.41

Abbreviations: ALL, acute lymphoblastic leukemia; BSA, body surface area; CI, confidence interval; NCI, National Cancer Institute; RR, relative risk.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using IBM SPSS statistics for Windows, Version 25.0. Demographics and treatment regimens were reported using descriptive statistics (tabulations, mean, median). Data from children with hepatic dysfunction was compared with those without hepatic dysfunction. Age, sex, type of ALL/LBL, NCI risk status, MRD status, and deaths were assessed using chi-squared tests. Body weight, body surface area (BSA), LDH, and uric acid parameters were assessed using Student's *t*-tests. Those variables with a *p*-value of < 0.2 were analyzed with multivariate regression analysis. Kaplan—Meier survival estimates were used to calculate the event-free survival (EFS) where death or relapse were considered as events. A *p*-value of less than 0.05 was considered as significant.

Ethics: The study was approved by the institutional ethics committee with number 05- 2022/194 on May 19, 2022. The study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

A total of 161 children were treated at our center between December 2013 and December 2021, of which 142 children underwent induction chemotherapy at our center as per the UK-ALL 2003 protocol and were included in the study. Out of 142, 118 (83%) children had B cell ALL, 20 (14%) had T cell ALL, 2 (1.4%) had B-LBL, and 2 (1.4%) had T-LBL. Ninety-three (65.4%) were boys and 49 (34.5%) were girls.

Seventy-three (51.4%) out of 142 children were categorized as standard risk and received three-drug induction, whereas 69 (48.2%) children were under the high-risk category and received four-drug induction.

Thirty-one (21.8%; 95% confidence interval [CI] 15.3–29.5) children developed hepatic dysfunction during induction chemotherapy as per the defined criteria which included 11 girls (22.5%) and 20 boys (21.5%; $p = 0.9$). Among the children under the age group of less than 10 years, 22 (19%) developed hepatic dysfunction (B-ALL 15, T-ALL 5, B-LBL 1, and T-LBL 1) as opposed to 9 (34.6%; B-ALL 7, T-ALL 2) children among those above 10 years of age ($p = 0.08$) (►**Table 1**).

Sixty-four patients (45%) received L-asparaginase and 10 (15.6%) of them developed hepatic dysfunction, whereas 67 (47.2%) patients received pegylated asparaginase and 18 (26.9%) of them developed hepatic dysfunction. Ten patients (7%) received both molecules of asparaginase at different time periods of induction and 2 (20%) developed hepatic dysfunction (*p* 0.29).

Seven (7/31; 22.5%) of them had hepatic dysfunction at presentation, of whom one patient with T-ALL presented with acute liver failure and hepatic encephalopathy—AST 3463 U/L, ALT of 1878 U/L, and total bilirubin/direct bilirubin (TB/DB) of 14.24/11.25 mg/dL. Two (2/31; 6%) of them had hepatic dysfunction in the first week of induction and five (5/31; 16.1%) each during the second and third weeks of induction therapy. Twelve (12/31; 38.7%) of them had hepatic derangements toward the end of induction between days 25 and 35.

Body weight, BSA, LDH levels, uric acid levels, and white blood counts at presentation are mentioned in ►**Table 2**—weight and BSA were significantly high in patients with hepatic dysfunction. But none of these parameters proved

Table 2 Table showing mean values of weight, BSA, LDH, uric acid, and WBC at presentation in two groups

Parameter	Hepatic dysfunction, yes		Hepatic dysfunction, no		*p*-Value
	Mean	SD	Mean	SD	
Weight	25.5	13.5	18.5	10.5	0.01
BSA	0.87	0.29	0.73	0.26	0.02
LDH	985	955.3	1074.4	1476.6	0.7
Uric acid	5.2	3.7	5.1	4.9	0.85
WBC at presentation	80316	145391	46068	81883	0.21

Abbreviations: BSA, body surface area; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cells.

to be significant risk factors for the development of hepatic dysfunction on multivariate analysis (►**Table 1**).

Among the 31 children with hepatic dysfunction, chemotherapy modification in terms of dose alteration or delay in administration was required in 14 (53.9%) children. Chemotherapy drug doses were modified in five children and a single dose of chemotherapy was omitted in four children in view of high bilirubin. Four children had a delay in administration of scheduled doses (average duration of 12.5 days) and in one child there was both delay in administration of chemotherapy as well as omission of doses.

►**Table 3** contains the data regarding the number of children in each category of hepatic dysfunction and their mean ages and ►**Table 4** contains the mean values of TB, DB, AST, and ALT.

Induction outcomes were measured in terms of end-of-induction MRD status. Out of 138 ALLs, MRD data was available for 123 patients (11 induction deaths, MRD data was not available for 4 patients)—20 in hepatic dysfunction and 103 in the group without hepatic dysfunction. Among the 20 children with hepatic dysfunction, 18 (90%) were MRD negative ($< 0.01\%$), and 2 (10%) were MRD positive ($> 0.01\%$),

Table 3 Distribution of patients among various subgroups of hepatic dysfunction, their mean ages, and number of children requiring chemotherapy modifications in each subgroup

Deranged parameters	Number (%)	Age (median ± SE)	Dose modification or delay, *n* (%)
Hepatic dysfunction	31 (21.8)	6 ± 0.86	14 (45.1)
AST/ALT elevation irrespective of TB/DB	14 (9.9)	5.5 ± 1.3	5 (35.7)
Isolated AST/ALT	4 (2.8)	3.75 ± 1.8	–
TB/DB elevation irrespective of AST/ALT	27 (19.0)	7 ± 0.94	12 (44.4)
Isolated TB/DB elevation	17 (12.0)	7 ± 1.2	7 (41.1)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DB, direct bilirubin; SE, standard error; TB, total bilirubin.

Table 4 Average values of various hepatic parameters

	Mean	SD	Median	Range (Q1–Q3)
AST (U/L)	197.3	634.3	0	0–202
ALT (U/L)	207.1	396.2	0	0–312
TB (mg/dL)	4.3	3.6	3.4	1.9–6.1
DB (mg/dL)	3.3	3.2	2.4	1.0–4.7
Age in years	7.6	4.8	6	3.5–11

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DB, direct bilirubin; SD, standard deviation; TB, total bilirubin.

whereas in the group with no hepatic dysfunction, 83 (80.6%) children had negative MRD and 20 (19.4%) children had positive MRD ($p = 0.31$). Among 18 children with a negative MRD in the hepatic dysfunction group, 8 received three-drug induction, and 10 received four-drug induction. Two patients who were MRD positive in the hepatic dysfunction group received four-drug induction.

A total of 37/142 (26%) children died in this cohort until the period of data collection—11/37 (29.7%) were during induction. Among the hepatic dysfunction group, 11/31 (35.4%) children died and 8/11 (72.7%) of them were during induction as opposed to 26/111 (23.4%) deaths among the group without hepatic dysfunction and 3/26 (11.5%) among them were during induction ($p < 0.001$). In the hepatic dysfunction group, 7/8 induction deaths were due to sepsis—2 children had multidrug-resistant (MDR) Gram-negative septicemia, 4 of them had MDR Gram-negative sepsis along with candida species infection, and 1 had culture-negative sepsis. Hepatic dysfunction in this set of children was preceded by sepsis. Acute liver failure at presentation was the cause of death in one child with T-cell ALL. Three other children died at later stages of treatment—two children died during maintenance chemotherapy—a 22-month-old child with chronic norovirus infection, a 10-year-old child with refractory congenital HLH (UNC13D defect), and another child died during consolidation therapy with septicemia.

Out of 23 patients who were alive at the end of induction in the hepatic dysfunction group, the data regarding the number of days taken for the resolution of dysfunction was available for only 18 patients, ranging from 5 to 45 days, with a median of 9.5 days.

In this cohort of 142 patients, a total of 15 children had a relapse of their disease until the time of data collection. None among the children with hepatic dysfunction had a relapse. Five-year EFS (death or relapse) was $59.93 \pm 9\%$ (95% CI: 40.2–75) in children with hepatic dysfunction as opposed to $72 \pm 5.0\%$ (95% CI: 59.1–78.8) in those without hepatic dysfunction (95% CI, $p = 0.07$) (►**Fig. 1**).

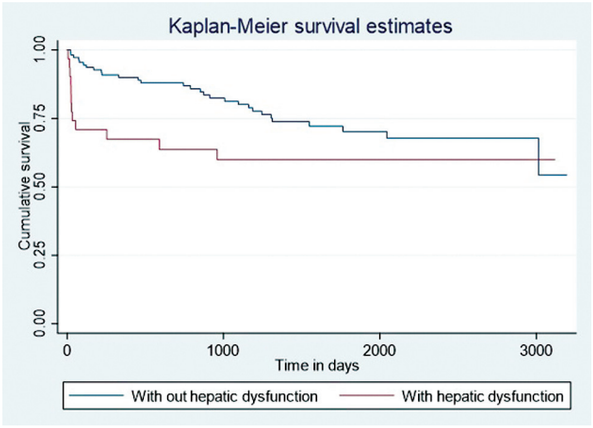

Fig. 1 Event-free survival in patients with hepatic dysfunction versus no hepatic dysfunction.

Discussion

Hepatic dysfunction during induction therapy was observed in 1 in 5 children at our center with a prevalence of 21.8% as opposed to a study by Denton et al where 6.8% hepatic dysfunction was seen during induction chemotherapy as per the Children's Oncology Group (COG) style modified Berlin-Frankfurt-Munich protocol.[10] Hashmi et al reported a 4% incidence of conjugated hyperbilirubinemia during early phases of chemotherapy as per the COG guidelines and 3.2% had transaminitis, whereas hyperbilirubinemia prevalence was 19% in our cohort and 9.9% had transaminitis.[11] These varying data from different centers could be attributed to the ethnicity and genetic makeup of the study population, variations in protocols, drug toxicity, and infection rates.

In our study, 4.9% of children (i.e., 7 out of 142) had hepatic dysfunction at presentation, of whom one child had fulminant hepatic failure and died on day 1 of induction. Fulminant hepatic failure has been reported at presentation in the past and was predominantly associated with poor outcomes.[12–14] In a study by Segal et al, 34% of children had elevated transaminases and 3.4% had hyperbilirubinemia at presentation.[15] This was attributed to the leukemic infiltrates in the liver and was substantiated by the findings of a significant association of hepatitis at presentation in patients with high leucocyte count, elevated LDH, and uric acid indicating an increased tumor burden. They treated these patients with a short course of steroids prior to the beginning of induction therapy. But in our cohort, we did not use any prephase steroids.

While obesity and age more than10 years were noted to be significant predictors of hepatic derangement in earlier reported studies, none of them were significant on multivariate analysis in our cohort.[10,11]

Though septicemia, HLH, leukemic infiltrates, and drugs are known causes of hepatic dysfunction and were evidenced in our study it was difficult to ascertain specific causes due to the retrospective nature of the study and lack of a structural workup. Mekonnen and Wondmeneh reported an incidence of moderate drug-induced hepatotoxicity to be 15% during ALL induction therapy.[16] While the drugs commonly used in induction specially asparaginase can cause hepatic dysfunction, voriconazole used for antifungal prophylaxis in regimen B can also cause hepatic derangements making the cause–effect association more difficult in a retrospective setting.

Induction mortality in those who developed hepatic dysfunction is high compared to those who did not ($p < 0.001$). Septicemia was the cause of mortality in all but one case in this group.

Chemotherapy modifications due to hepatic dysfunction were done as per the UK-ALL 2003 protocol. In our cohort, close to 1 in 2 children with hepatic derangements during induction therapy (14/31) required some form of chemotherapy modification—delay/reduction in dose/omission. This was very high as compared to the cohort by Denton et al where 1 in 6 children with induction toxicity (hepatic + pancreatic) required drug modifications.[10] They did not observe any effect on overall survival due to drug modifications. The 5-year EFS in our cohort was lower in patients with hepatic dysfunction compared to no hepatic dysfunction

($p = 0.07$) as opposed to Denton et al where treatment-related toxicity did not affect the EFS.[10] Sepsis-related induction deaths must have contributed to this dismal EFS in our patients with hepatic dysfunction.

Though the MRD outcomes in both the groups were not statistically different and there were no relapses in the hepatic dysfunction group, these must be interpreted with caution as the induction mortality was high in the hepatic dysfunction group.

A large prospective study with a structured workup for ascertaining specific causes for deranged hepatic functions will provide more comprehensive data and should be considered.

Conclusion

One in five children with ALL and LBL had hepatic dysfunction during induction therapy. Induction mortality is high in those with hepatic dysfunction compared to those with normal liver function, with sepsis being the most common cause of death in our settings. It is difficult to ascertain the cause of hepatic dysfunction in a retrospective study due to multiple confounding factors. Though modifications due to hepatic dysfunction did not seem to affect the induction outcomes in the hepatic dysfunction group, this should be interpreted with caution due to the high induction mortality in that group and the small sample size.

Patient Consent
None declared.

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

Authors' Contributions
N.A.R.: Contributed to conception of design, literature search, data collection, data and statistical analysis, manuscript writing, editing, and manuscript review.
K.R.: Contributed to data collection, literature search, and manuscript review.
H.P.L.: Contributed to conception of design, data and statistical analysis, manuscript editing, and manuscript review.

Sources of Support
None declared.

Funding
None declared.

Conflict of Interest
None declared.

Acknowledgments
None declared.

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Clinical Profile of Male Patients Presenting with Breast Cancer in Kashmir Valley

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Ind J Med Paediatr Oncol 2024;45:153–156.

Abstract

Introduction Breast cancer is a rare disease in males with unknown etiology and variable rate of incidence among different ethnic and geographical groups.

Objectives This article studies the clinical profile of male breast cancer in Kashmir Valley of India

Materials and Methods This study was a retrospective study conducted at a super-specialty hospital (Government Medical College Srinagar) in the department of medical oncology over a period of 4 years from January 2017 to October 2021. All male patients who presented with a histopathology-proven diagnosis of breast cancer were included and studied.

Results A total of 8 male patients with breast cancer were studied. The median age at diagnosis was 55 years. Most of the patients were from rural background. The most common presenting symptom was breast lump followed by ulceration. The most common location of the tumor was retroareolar. Infiltrating ductal carcinoma (100%) was the only subtype present in our patients. Locally advanced disease accounted for most of the cases. Among stage IV patients two had bone as the metastatic site and one patient had in addition lung metastasis. Immunohistochemistry analysis revealed that all patients (100%) were hormone receptor positive with only one patient being triple positive (12.5%). None of the patients had triple negative disease in our study. In our study 6 patients were treated with multimodalities (surgery, chemo, radiation, and targeted agents).

Conclusion Male breast cancer is a well-recognized entity and the gender gap of disease need to be abolished. Awareness among masses and training of general practitioners is needed to pick cases at early stage.

Keywords
- male breast cancer
- triple negative
- ductal carcinoma
- lung metastasis

Introduction

Male breast cancer is a rare disease occurring in the breast tissue of men and is uncommonly encountered in routine practice by an oncologist. Breast cancer is considered as the disease of female breast due to its high incidence in females, but breast cancer does occur in men. The disease can occur at any age, but most commonly seen in elderly population. Male breast cancer accounts for less than 1% of all cancers in men

article published online
March 21, 2024

DOI https://doi.org/10.1055/s-0043-1777354.
ISSN 0971-5851.

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

and less than 1% of all diagnosed breast cancers.[1] The low incidence rate of breast cancers in men compared with female account to lesser amount of their breast tissue and associated difference in hormonal effect. Even though the factors that influence the malignant changes are the same. The incidence of male breast cancer is variable in different ethnic and geographical groups[2,3]. In Europe it is approximately 1/100,000 as compared with < 0.5/100,000 in Japan[4] In Central African countries the breast cancer rate is $> 6\%$ in men,[3,5] which could be due to hyperestrogenism caused by endemic hepatic infectious disease.[3,6] The etiology of male breast cancer is unknown, although many factors have been implicated in the risk factors of male breast cancer, but in clinical practice, increased age is the only factor to have strong association.[7]

Positive family history plays a role in the risk of male breast cancer more so in metastatic stage, approximately 15 to 20% cases.[6] Both BRCA1 and BRCA2 mutations are implicated, more so BRCA.[2,8] Males with Klinefelter's syndrome carry XXY chromosomal anomaly and have approximately 20- to 50-fold increased lifetime risk of breast cancer.[3,5] Occupational exposures such as blast furnaces, steel works,[6] and men working with soap and perfume petrol[9,10] have been associated with increased risk of breast cancer. Other occupational exposures have also been implicated but conclusive evidence is lacking. Radiation exposure has been also implicated with a dose relationship to disease. Low radiation dose exposure has not been found to be causative, but higher dose exposure as used in the treatment of gynecomastia and survivors of atomic bomb exposure have been found to have increased relative risk of developing breast cancer.[12,13]

Endocrine imbalance (estrogen/testosterone) tip the male to increased risk of breast cancer and conditions with increased estrogen level like diseases affecting the testis.[14] Obesity[14,15] and exogenous estrogen use in cancer prostate in the past[16] also have increased risk. Male breast cancer cases are especially from rural and low socioeconomic status and present late with an advanced stage. Although male breast cancer is not more aggressive than female breast cancer and have better prognosis due to its biology (most are hormone receptor positive) when compared with same age and stage female breast cancer. Despite this, it is an unfortunate scenario that elderly male patients shy away to approach health care for treatment till they present with huge fungating growth. Due to relative rarity of male breast cancer, prospective randomized trials are lacking and most information on breast cancer in men is collected from retrospective studies of several decades and treatment recommendations have been extrapolated from results of trails in female patients.[14,17]

Material and Methods

The current study was a retrospective study conducted at a superspecialty hospital (an associated hospital of Government Medical College Srinagar) in the department of medical oncology, over a period of 4 years from January 2017 to October 2021. All male patients who presented with a histopathology-proven diagnosis of cancer breast were included and studied. Patients who presented with cytological diagnosis and no histopathology-proven confirmation were excluded from the study. Detailed history with focus on risk factors and clinical features were retrieved from departmental records of all patients, staging workup including core biopsy with immunohistochemistry (IHC) (ER, PR, Her2, Ki67) and if bilateral mammography had been performed. Contrast-enhanced computed tomography chest and abdomen and bone scan had been performed as and when required, also TNM staging and magnetic resonance imaging breasts had been done in patients who presented as axillary swelling without a primary breast swelling. Histopathological profile with focus on grade of tumor, receptor status, type of tumor, and lymphovascular invasion had been taken into consideration. Different modalities of treatment availed by patients were analyzed. The data was analyzed for various clinicopathological features and acceptance to different modalities of treatments of male breast cancer.

Results

A total of 8 patients were diagnosed as male breast cancer and reported to the department of medical oncology of this hospital during the study period of 4 years. The youngest patient was 42 years old and the oldest was 83 years old. The median age at diagnosis was 55 years. Six (75%) patients were more than 55 years and 2 (25%) were less than 55 years of age. Most of the patients (6, 75%) were from rural background. Left side lesions (6 out of 8, 75%) were more common than right side lesions (2 out of 8, 25%). The most common presenting symptom was breast lump (75%), skin ulceration (25%), and axillary lump (25%). None of the patients had any association with known risk factors except age. The most common location of the tumor was retroareolar (70%). Infiltrating ductal carcinoma (100%) was the only subtype present in our patients. The tumor was mostly low (grade 1) 50% and moderate (grade 2) 37.5%, only 12.5% had high (grade 3) tumor.

In our study, locally advanced disease accounts to (6 out of 8) 75% which was equally distributed between stage II and stage III (3) 37.5% each and (2) 25% were in stage IV disease, respectively. Among stage IV patients both had bone as the metastatic site and one patient in addition had lung metastasis. IHC analysis revealed that all patients (100%) were hormone receptor positive with only one patient being triple positive (12.5%). None of the patients had triple negative disease in our study. All 6 patients in our study with locally advanced disease had been worked up for complete staging and had been treated with multimodalities (surgery, chemotherapy, radiation, and targeted agents [hormonal, trastuzumab [1]]). Both (2) stage IV patients received only hormonal treatment and denied any surgical intervention (toilet mastectomy) plus palliative radiation to bone. These 2 stage IV patients expired on follow-up. All 6 patients with locally advanced disease have been on follow-up till date (►**Table 1**). All 6 patients with locally advanced disease received four cycles of AC (doxorubicin plus cyclophosphamide) followed by 12 weekly doses of paclitaxel chemotherapy.

Table 1 Clinicopathological characteristics of patients

Parameters	Number (*n*)		Percentage
Age	< 55 y	6	75
	> 55 y	2	25
Demographics	Rural	6	75
	Urban	2	25
Presentation	Breast lump	6	75
	Axillary lump	2	25
	Skin ulceration	2	25
Histopathology	Infiltrating ductal carcinoma	8	100
	Other histological subtypes	0	
Family history and association with other risk factors	Present	0	0
	Absent	8	100
Tumor grade	G-1	4	50
	G-2	3	37.5
	G-3	1	12.5
Stage	I	0	0
	II	3	37.5
	III	3	37.5
	IV	2	25
IHC	Hormone receptor positive	8	100
	Triple positive	1	12.5
	Triple negative	0	0
Site of metastasis	Bone	2	100
	Bone and lungs	1	50
	Liver, brain, and soft tissue	0	0

Abbreviation: IHC, immunohistochemistry.

Discussion

The prevalence of male breast cancer increases with age and is rarely seen before the age of 40 years. The median age observed in our study was 55 years at the time of diagnosis. It is similar as reported in the literature. It has been observed that almost in all studies male breast cancers are diagnosed at 5th to 7th decades of life.[3,4] In our study, the most common symptom was breast lump (75%).[18] In our study, an isolated axillary lump was a significant presentation and this finding needs more extensive studies. Positive family history and associated risk factor have been involved in increased risk of developing male breast cancer but none of our patients had any such association. All 8 (100%) patients in our study had infiltrating ductal carcinoma in histopathological exam which is in accordance with as reported in other studies.[19]

Most of the patients 4 (50%) in our study had grade 1 tumors unlike other studies reporting grade 2 tumors as the common.[20] Out of 8 patients 6 (75%) were in stage II and III (37.5%) each, while other studies report majority with stage II disease.[21] This variation may be attributed to small sample size and other geographical and ethnic factors and needs further study. In our study, all 8 (100%) patients were hormone receptor (ER, PR) positive, only 1 (12.5%) patient was triple positive and none was triple negative. Male breast cancer receptor status of our study has almost similar findings with others studies.[21,22] In our study, high grade and advanced stage tumors present with distant metastasis to the bone (100%), and bone and lung in 50% patients in males > 75years of age.[23]

As far as the treatment part of male breast cancer is concerned, multimodality treatments are available. Hormone treatment is an important part of all male breast cancer treatment as all are hormone receptor positive. Surgery in the form of modified radical mastectomy is done for stage I to III, radiotherapy is given in high-grade and locally advanced tumors.

Conclusion

Male breast cancer is an uncommon disease but is a well-recognized entity. Breast cancer has always been considered as a disease of female gender. The gender gap of the disease needs to be abolished. Younger males because of awareness

present at an early stage and are eager to get treatment. Hence, younger males fare well in their disease course. Elderly males especially from rural background present at an advanced stage due to delayed presentation. Elderly male population lacks awareness and also shies away from the disease, resulting in their reluctance for treatment. To raise awareness among masses about the disease is required and general practitioners also need to be educated so that cases are picked at early stage for better outcome. However, large sample studies are the need of the hour to draw more conclusions regarding modalities of treatment.

Patient Consent
None declared.

Conflict of Interest
None declared.

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PD-L1 Testing and Assessment: Practical Considerations for Oncologist and Pathologist

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Ind J Med Paediatr Oncol 2024;45:157–162.

Introduction

Recently, immunotherapy with anti-PD-1(programmed cell death protein 1) or anti-PD-L1 (programmed cell death ligand 1) antibodies has shown both favorable and durable responses in a subset of patients with metastatic and advanced cancers. Although no robust predictive biomarker for immune checkpoint inhibitors (ICI) has been established till date, PD-L1 immunohistochemistry (IHC) testing has emerged with a passable utility. However, PD-L1 is still far from being a perfect biomarker. Nevertheless, PD-L1 testing by IHC to evaluate the immunoexpression of PD-L1 protein in tumor cells and/or immune cells is a useful predictive biomarker for predicting response to ICI.[1–4]

Types of PD-L1 IHC Assays and Scoring

In oncology practice, the three most commonly used PD-L1 IHC assays, their respective PD-L1 antibodies, and associated IHC platforms are 22C3 (Dako), SP142 (Ventana), and SP263 (Ventana). A particular PD-L1 antibody clone and its associated platform have been approved by U.S. Food and Drug Administration (FDA) for respective ICI (PD-1 and PD- L1 inhibitor) intended for a particular malignancy type. Moreover, the approval also takes into account the type of cells expressing PD-L1, based on which the following three types of scoring (►**Figs. 1–8**) have been developed:

1. **Tumor Proportion Score (TPS)**: It is scored as percentage of tumor cells showing distinct membranous staining. TPS is frequently utilized for metastatic non-small cell lung carcinoma (NSCLC). A potential misinterpretation can occur due to known membranous immunostaining of native pneumocytes or reactive histiocytes, which can be erroneously included in TPS (►**Fig. 7**). Hence, correlation with histomorphology is prudent for accurate scoring.
   TPS (%) = PD-L1 positive tumor cells x 100 Total tumor cells (PD-L1 positive + PD-L1 negative tumor cells)
2. **Immune Cells Staining (ICS):** It is scored as the percentage of tumor area that is occupied by PD-L1-stained immune cells of any intensity. ICS is commonly utilized for metastatic triple negative breast cancer and urothelial carcinoma. The scoring is done on immune cells only within tumor micro environment (►**Fig. 3**). Areas of necrosis and granulation tissue should not be considered or sampled for assessment.
3. **Combined Positive Score (CPS):** It is scored as number of PD-L1-stained cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. It is expressed in numbers and not in percentage, as it may exceed 100. CPS is frequently utilized for metastatic and recurrent head and neck squamous cell carcinoma as well as metastatic gastric/gastroesophageal adenocarcinoma (►**Fig. 4**).

article published online
November 28, 2022

DOI https://doi.org/10.1055/s-0042-1748797.
ISSN 0971-5851.

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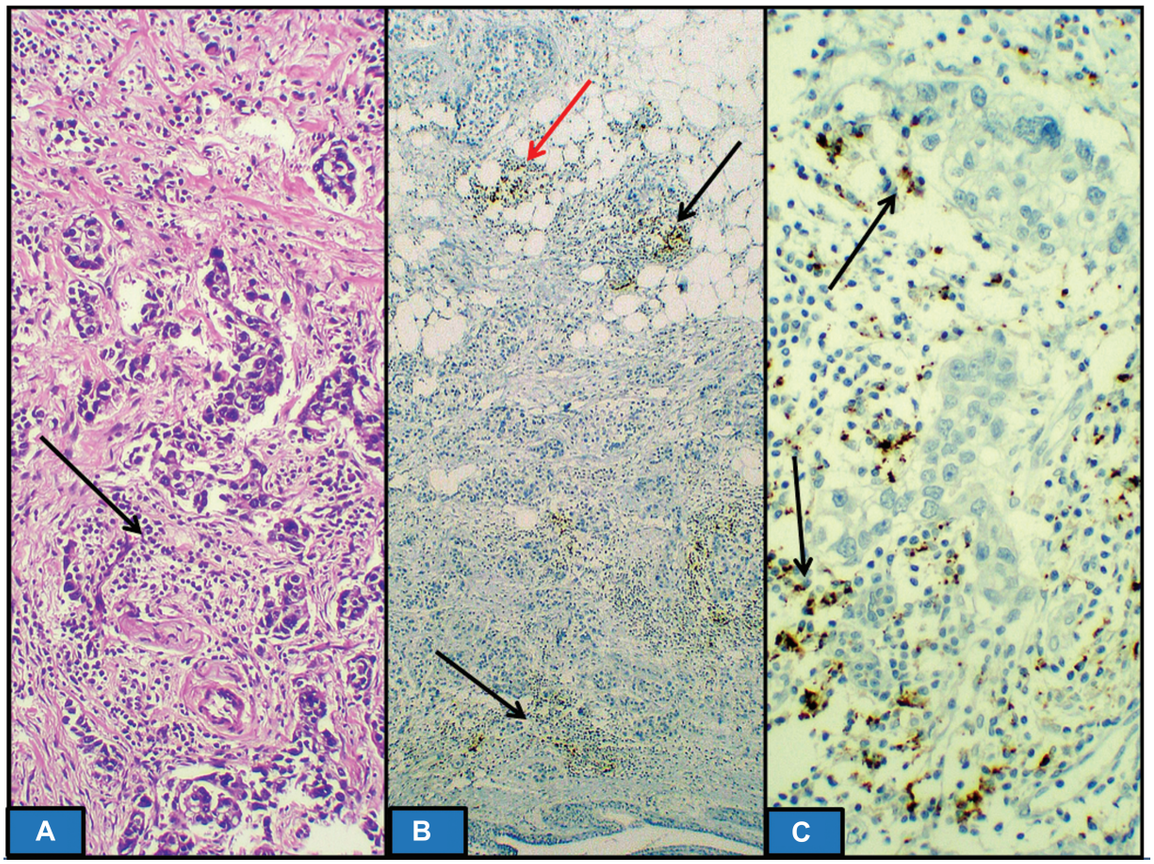

Fig. 1 (**A**) Hematoxylin and eosin sections showing metastatic grade III, triple negative breast cancer in axillary lymph node with immune cells in tumor microenvironment (TME) (black arrow). (**B** and **C**) Programmed cell death protein ligand 1 (PD-L1) (SP142) immunohistochemistry showing immune cells staining (ICS) score of 5%. The ICS in TME only should be taken into consideration. PD-L1 staining in immune cells away from TME (red arrow) not in contact with tumor cells is not to be considered.

CPS= PD-L1 immunostained cells (tumor cells, lymphocytes, macrophages) $\times$ 100
Total viable tumor cells

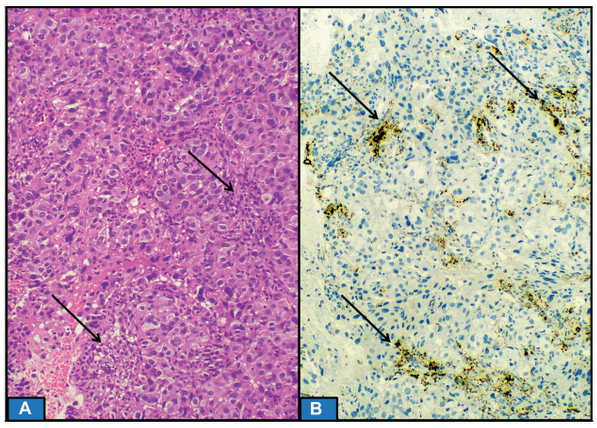

Fig. 2 (**A**) Hematoxylin and eosin sections showing primary breast invasive duct carcinoma, grade III, (triple negative breast cancer) with immune cells (TILS) in tumor microenvironment (arrow). (**B**) Programmed cell death protein ligand 1 (SP142) immunohistochemistry showing immune cells staining score of 20% (arrow). TILS: tumor infiltrating lymphocytes.

Clinical Setting for PD-L1 IHC Testing

1. **Companion Diagnostic Test**: It is a prerequisite or mandatory test that provides information for the effective and safe use of an intended therapeutic drug. The various companion diagnostic PD-L1 assays with details are listed in ►**Table 1**.
2. **Complementary Diagnostic Tests:** It is not a mandatory test before initiating the treatment with intended drug; however, it aids in the therapeutic decision. For example, Ventana SP142 PD-L1 assay is used as a complementary diagnostic test for intended treatment with Atezolizumab in previously treated NSCLC if TPS $\geq$ 50% or IC score $\geq$ 10%.

Laboratory Developed Tests (Interconvertibility of Assays)

FDA-approved/CE-marked PD-L1 assays are validated assays in clinical trials. Any assay/test other than these assays are known as laboratory developed tests (LDT), also known as "Fit for purpose" testing. This is advocated, as a single laboratory cannot establish multiple IHC platforms. LDTs are difficult to achieve as they require adequate validation

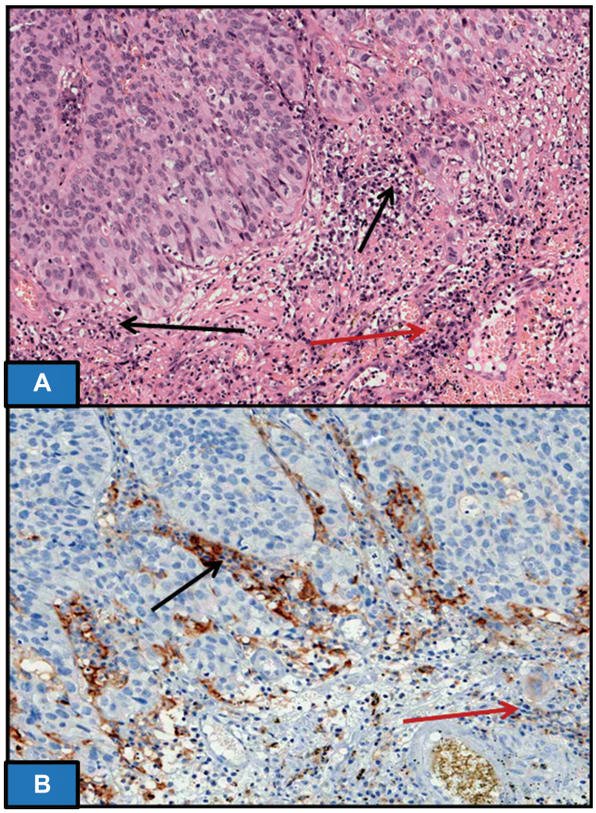

Fig. 3 (A) Hematoxylin and eosin section showing high-grade urothelial carcinoma of bladder with immune cells in tumor microenvironment (TME) (arrow). (B) Programmed cell death protein ligand 1 (SP142) immunohistochemistry showing immune cells staining score of 25% (black arrow). The immune cells away from TME (red arrow) will not be taken into consideration. No membranous staining seen in tumor cells.

against an appropriate standard. LDT is developed by the laboratory with FDA-approved tests and concordance of >90% is required as validation.[1,2]

Specimen Type, Adequacy, and Factors Affecting Accuracy of Test

- The PDL-1 immunoexpression results vary spatiotemporally, and hence the most recent tumor specimen, whenever available and feasible, may be utilized for testing for patient selection.
- The tissue should be fixed in 10% neutral buffered formalin for optimal results.
- The storage time for paraffin blocks used for testing should preferably be less than 3 years.
- There should be no diffidence in using cell blocks for the evaluation of TPS in NSCLC, as several cases of NSCLC are diagnosed on malignant pleural effusion. Minimum 100 viable tumor cells are required for TPS evaluation in both cell block and tru-cut biopsy. Blueprint study (Phase 2b)

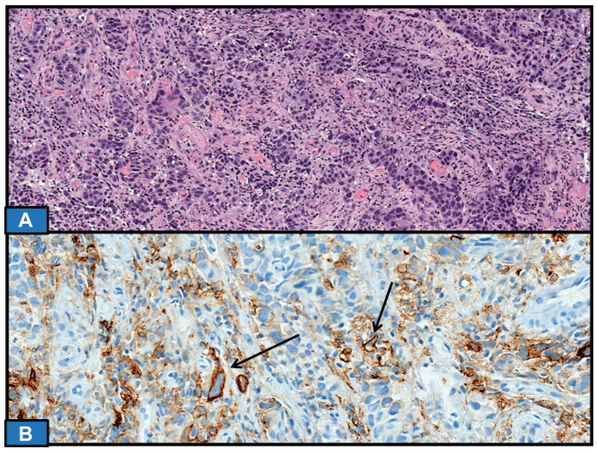

Fig. 4 (A) Hematoxylin and eosin section showing poorly differentiated adenocarcinoma of stomach. (B) Programmed cell death protein ligand 1 (PD-L1) immunohistochemistry showing CPS of 40. The high score is attributed to immune cells displaying PD-L1 staining, while very few tumor cells show membranous positivity (arrow).

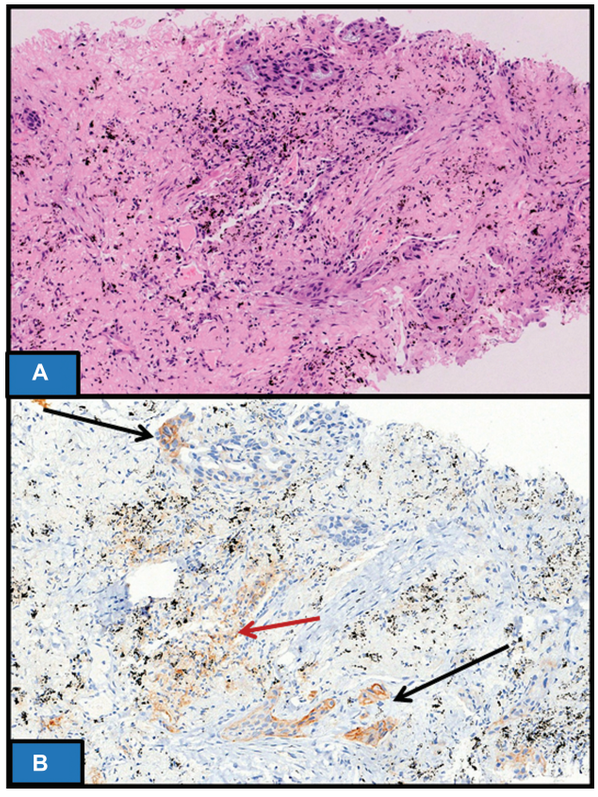

Fig. 5 (A) Hematoxylin and eosin section showing non-small cell lung carcinoma in a tru-cut biopsy. (B) Distinct membranous programmed cell death protein ligand 1 immunoexpression (tumor proportion score) in 5% of tumor cells of weak intensity (black arrow). Immune cells staining (red arrow) will not be taken into consideration.

has proven the harmonization of TPS in tru-cut biopsy, cell blocks, and resection specimens for NSCLC. However, cell blocks are not suitable for ICS and CPS evaluation.[5]

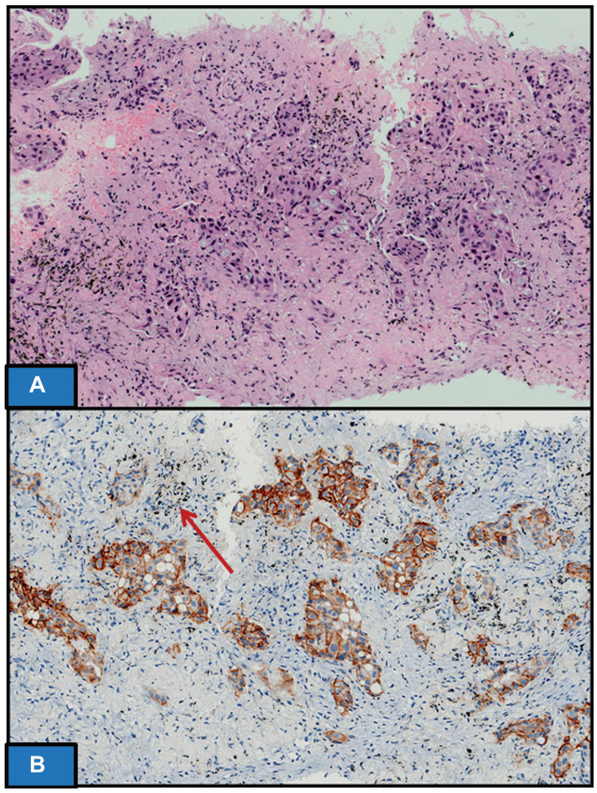

Fig. 6 (A) Hematoxylin and eosin section showing non-small cell lung carcinoma in a tru-cut biopsy. (**B**) Distinct membranous programmed cell death protein ligand 1 immunoexpression (tumor proportion score) in 90% of tumor cells of moderate to strong intensity. Immune cells staining (red arrow) will not be taken into consideration.

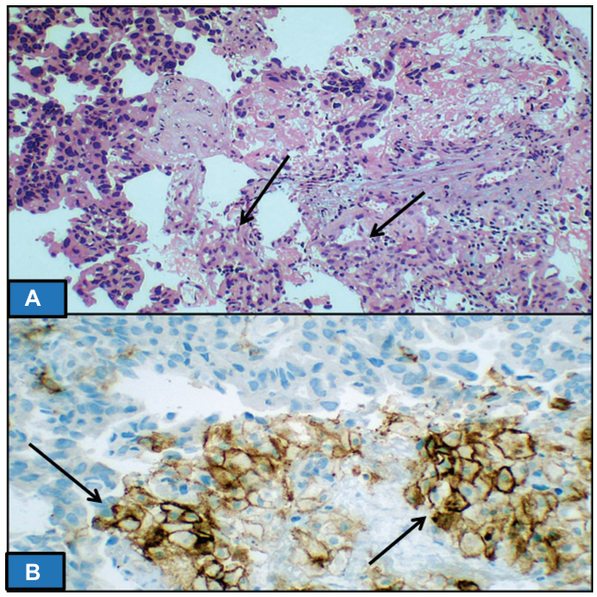

Fig. 7 (A) Hematoxylin and eosin section showing tru-cut biopsy with non-small cell lung carcinoma with adjoining areas of histiocytes (arrow). (**B**) Distinct membranous programmed cell death protein ligand 1 immunoexpression in histiocytes that can be erroneously taken as positive tumor cell staining. Note that the size of nucleus of histiocytes is significantly smaller than the tumor nucleus (upper half unstained), and this serves as a clue to differentiate between the two.

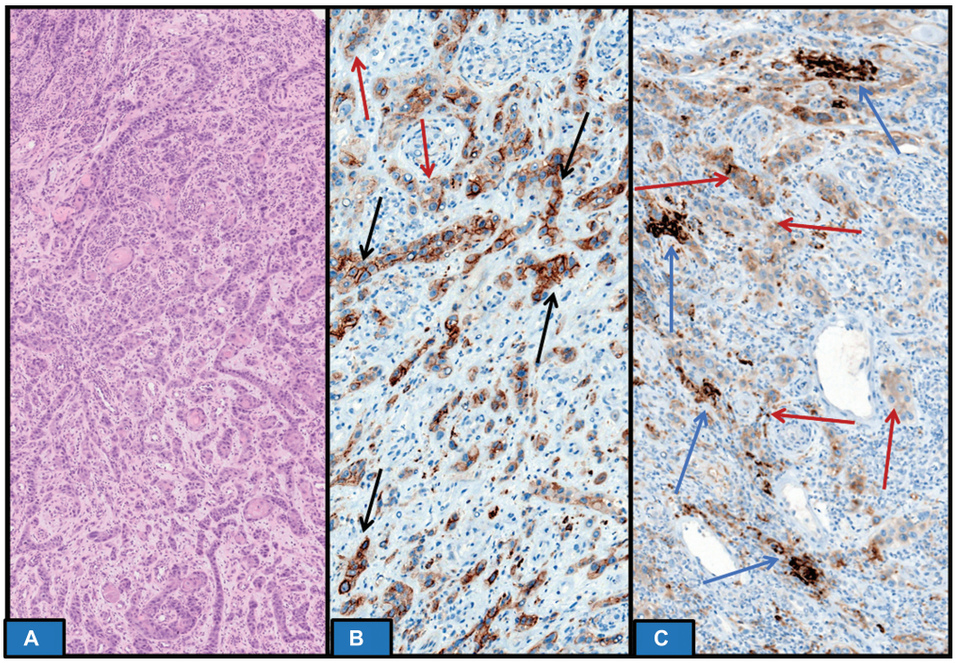

Fig. 8 (A) Hematoxylin and eosin section showing recurrent locally advanced head and neck squamous cell carcinoma. (**B** and **C**) Programmed cell death protein ligand 1 immunoexpression is heterogenous. Few areas show partial and complete distinct membranous staining (black arrow) in tumor cells to be included in scoring. Significant tumor cells show cytoplasmic staining without membranous accentuation (red arrow), which is not to be counted in scoring. Immune cells staining is very less (blue arrow); however, it will be included in scoring. The final CPS was 25.

Table 1 List of FDA/CE marked approved companion of diagnostic PD-L1 assay for intended use of ICI in various malignancies and their respective immunoexpression with their cutoff threshold

Type of malignancy and affected organ	Intended ICI and line of therapy	Companion of diagnostic PD-L1 assay	Type of scoring for PD-L1 immunoexpression	Approving agency
NSCLC (metastatic/UR stage III, NE for definite CT/RT)	Pembrolizumab (anti-PD-1) 1st line monotherapy	22C3 (Dako)	TPS; $\geq$ 50%	FDA
NSCLC (metastatic/UR stage III, NE for definite CT/RT)	Pembrolizumab (anti-PD-1) 1st line monotherapy	SP263 (Ventana)	TPS; $\geq$ 50%	CE marked
NSCLC (Metastatic)	Pembrolizumab (anti-PD-1) 2nd line monotherapy	22C3 (Dako)	TPS; $\geq$ 01%	FDA
Urothelial carcinoma (LA/metastatic NE for CT)	Atezolizumab 1st line monotherapy	SP142 (Ventana)	ICS; $\geq$ 05%	FDA
Urothelial carcinoma (LA/metastatic NE for CT)	Pembrolizumab 1st line monotherapy	22C3 (Dako)	CPS; $\geq$ 10	FDA
TNBC (recurrent LA/metastatic)	Atezolizumab 1st line, in combination with nab-paclitaxel	SP142 (Ventana)	ICS; $\geq$ 01%	FDA
TNBC (recurrent LA/metastatic)	Pembrolizumab (anti-PD-1) 1st line, in combination with nab-paclitaxel	22C3 (Dako)	CPS; $\geq$ 10	FDA
Gastric/GEJ adenocarcinoma (recurrent LA/ metastatic)	Pembrolizumab (anti-PD-1) 3rd line monotherapy	22C3 (Dako)	CPS; $\geq$ 01	FDA
Cervical carcinoma (recurrent LA/ metastatic)	Pembrolizumab (anti-PD-1) 2nd line monotherapy	22C3 (Dako)	CPS; $\geq$ 01	FDA
Esophagus SCC (recurrent LA/metastatic)	Pembrolizumab (anti-PD-1) 2nd line /3rd line monotherapy	22C3 (Dako)	CPS; $\geq$ 10	FDA
HNSCC (metastatic/recurrent/UR)	Pembrolizumab (anti-PD-1) 1st line monotherapy	22C3 (Dako)	CPS; $\geq$ 01	FDA

Abbreviations: CE, European Conformity; CT, chemotherapy; CPS, combined positive score; FDA, U.S. Food and Drug Administration; HNSCC, head and neck SCC; ICI, immune checkpoint inhibitor; LA, locally advanced; NE, not eligible; NSCLC, nonsmall cell lung carcinoma; PD-L1, programmed cell death protein ligand 1; RT, radiation therapy; SCC, squamous cell carcinoma; TNBC, triple-negative breast cancer; UR, unresectable.

- Decalcified tissues (bone metastatic site) are also not recommended for PD-L1 evaluation.
- Satisfactory positive and negative PD-L1 controls should be taken on the same slide before interpretation of test (►**Fig. 9**).
- Regular participation in External Quality Assurance Scheme and Proficiency testing ensures accuracy and reproducibility of test results.[1,5]

Limitations of PD-L1 Testing and Future Perspectives

Although PD-L1 testing remains the most common predictive biomarker in current oncology practice, it is still an imperfect biomarker as some patients who are PD-L1 negative may still respond to ICI while those who are positive may not respond to ICI. The other challenge is intra- and intertumoral heterogeneity for PD-L1 immunoexpression that has implications in scoring and PD-L1 results. Moreover, with recent strategies to combine ICI with chemotherapy, it may further limit the precise significance of predictive utility of PD-L1 testing. A close collaboration between oncologist and pathologist is essential and further prospective large randomized trials are required to establish the precise role of biomarkers, especially PD-L1 for predicting response to ICI.[3,4]

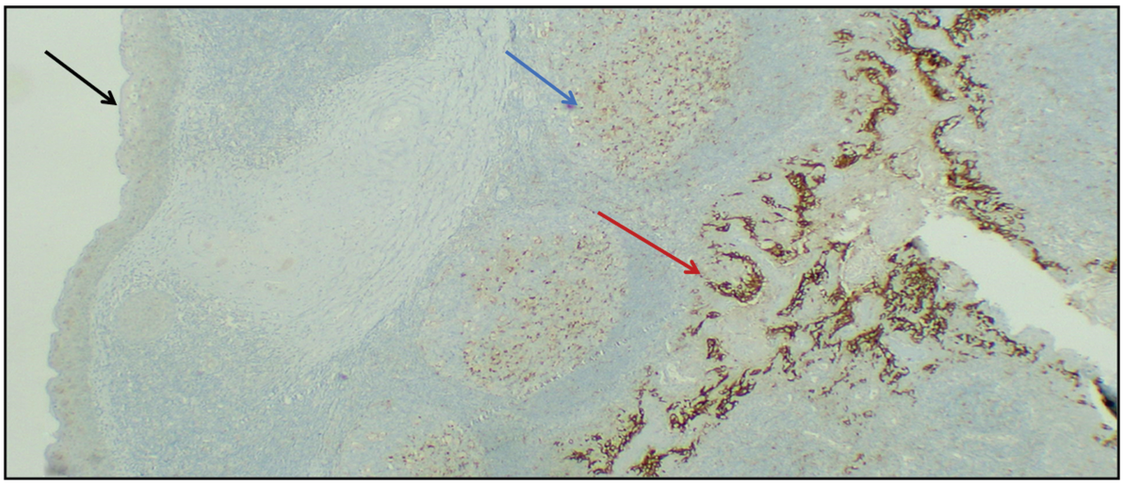

Fig. 9 On-slide positive and negative control (tonsillar tissue). The cryptic epithelium showing strong membranous positivity (red arrow), the surface epithelium is negative (black arrow), and the germinal centers show granular staining of moderate intensity (blue arrow).

Source of Support
None declared.

Conflict of Interest
None declared.

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Plasma Cell Neoplasm with Clear Cell Morphology—A Diagnostic Dilemma

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Ind J Med Paediatr Oncol 2024;45:163–164.

Keywords
- Clear cell plasmacytoma
- pleural cavity
- dilemma
- immunohistochemistry
- CD138

Apart from their usual morphology (eccentrically placed round to ovoid nuclei with cart-wheel-like chromatin, perinuclear halo and deep basophilic cytoplasm), very rarely plasma cells show varied appearances—signet-ring, pleomorphic, blastic, vacuolated, spindle cell, and clear cell.[1] Here, we present a case of plasmacytoma involving the right pleural cavity with unusual morphology and masquerading as a nonhematolymphoid neoplasm.

A 75-year-old woman presented with complaints of weakness, shoulder, and back pain with breathlessness. Magnetic resonance imaging (MRI) of the thoracic spine (►**Fig. 1A**) showed a heterogeneous lesion measuring $11.3 \times 2.5 \times 3.9$ cm in the right pleural cavity with involvement of the adjacent ribs, costovertebral joints, and infiltration of the right neural foramina in the T3 to T4 and T4 to T5 regions. The lesion showed low fluorodeoxyglucose (FDG) uptake on positron emission tomography-computed tomography (PET-CT) scan with standardized uptake value (SUV) max of 3.3.

Needle core biopsy of the lesion under ultrasound guidance was done. Histopathological examination revealed fibrocollagenous tissue and skeletal muscle bundles with neoplastic cells arranged in cords and sheets (►**Fig. 1B**). The

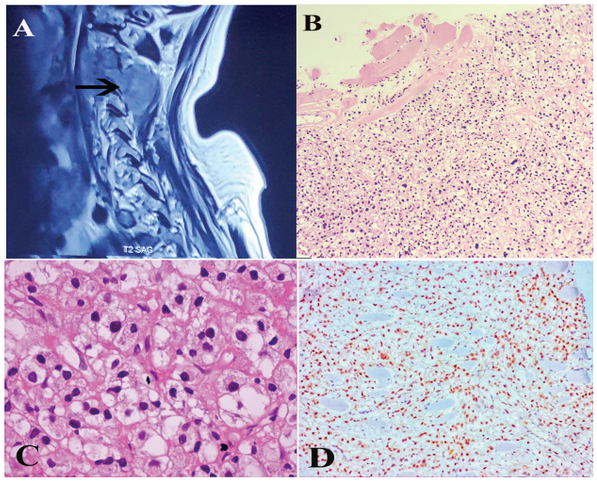

Fig. 1 (**A**) Magnetic resonance imaging of thoracic spine showing a large heterogeneous lesion involving the pleural cavity. (**B**) Hematoxylin and eosin (H&E) section shows skeletal muscle bundles with neoplastic cells arranged in cords and sheets, 200x magnification. (**C**) Individual cells showing ovoid nuclei with clumped chromatin and moderate amounts of vacuolated to clear cytoplasm, H&E 400x magnification. (**D**) Strong and diffuse nuclear staining for MUM1 immunostain, 200x magnification.

article published online
July 5, 2023

DOI https://doi.org/10.1055/s-0043-1770786.
ISSN 0971-5851.

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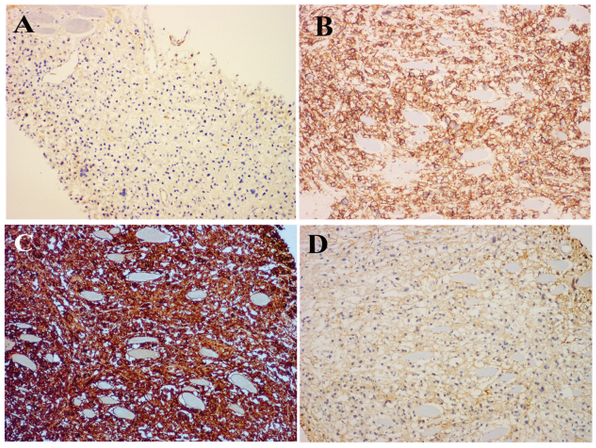

Fig. 2 (**A**) Pancytokeratin immunohistochemistry exhibiting no staining of the neoplastic cells, 100x magnification. (**B**) Strong and diffuse membranous staining for CD138 immunostain, 200x magnification. (**C**) Strong and diffuse cytoplasmic staining for lambda light chain immunohistochemistry (IHC); 200x magnification. (**D**) Kappa light chain IHC: No staining of the neoplastic cells, 200x magnification.

individual cells exhibited moderately pleomorphic ovoid nuclei with clumped chromatin and moderate amounts of vacuolated to clear cytoplasm (►**Fig. 1C**). A diagnosis of malignant neoplasm was rendered with differentials of mesothelioma, PEComa, clear cell renal cell carcinoma, and poorly differentiated carcinoma. Immunohistochemistry (IHC) with a panel of markers was performed.

The neoplastic cells were negative for pancytokeratin (►**Fig. 2A**), WT1, TTF1, PAX8, HMB45, S100, CD34, MelanA, desmin, caldesmon, SMA, SOX10, and TFE3. They showed strong and diffuse membranous staining for CD138 (►**Fig. 2B**), moderate and diffuse nuclear staining with MUM1 (►**Fig. 1D**), strong and diffuse cytoplasmic staining for lambda light chain (►**Fig. 2C**), and no cytoplasmic staining for kappa (►**Fig. 2D**); the cells also exhibited weak nuclear staining for estrogen receptor. A final diagnosis of plasmacytoma was made. Further workup for multiple myeloma was advised but the patient succumbed soon after.

Clear to vacuolated cytoplasm, centrally placed nuclei with clumped chromatin and no perinuclear hof are extremely unusual in neoplastic plasma cells. To our knowledge, this is the first case with this morphology involving soft tissue. It has previously been hypothesized to be artifactual, pertaining to decalcification of bone marrow samples.[2,3] However, our case involved biopsy of soft tissue that did not undergo decalcification. Švec et al hypothesized that accumulation of misfolded proteins and formation of autophagic vacuoles in neoplastic plasma cells can account for clear cell change.[4]

We, thus, recommend that this entity be kept in mind during the workup of a neoplasm with clear cell morphology in soft tissue and include study of light-chain restriction when other immunohistochemical markers are overlapping or noncontributory.

Conflict of Interest
None declared.

Acknowledgement
The authors would like to thank Dr. Sanjay Pai of Manipal Hospital, Yeswanthpur, Bengaluru, for his valuable opinion and advices.

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Trends in Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: Lessons for Resource-Challenged Regions

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Ind J Med Paediatr Oncol 2024;45:165–166.

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Swan et al report the trends in autologous hematopoietic stem cell transplantation (ASCT) for newly diagnosed multiple myeloma over the past three decades in the European Society for Blood and Marrow Transplantation (EBMT) centers.[1] The stem cell utilization rates (STUR) of ASCT for myeloma have shown a rising trend for most resource-rich regions (13 to 24% in Northern America and 15 to 22% in Europe).[2] However, we would like to focus on the trends in treatment-related mortality (TRM) that has important lessons for resource-challenged regions. The TRM rates from ASCT reported in the EBMT centers show a downward trend over the past three decades from approximately 5 to 1%.[1] The same in the US centers is down from approximately 3 to less than 1%.[3,4] Trends in increasing STUR parallel decreasing TRM for ASCT in multiple myeloma. ASCT is the standard of care in the treatment paradigm of eligible myeloma patients.[5,6] Undoubtedly, there is a progression-free survival (PFS) benefit to multiple myeloma patients with ASCT as reported in meta-analysis; however, no overall survival benefit was observed.[7,8] The data on PFS benefits are drawn from landmark randomized controlled studies in resource-rich countries. With the current standard dose therapy (SDT) comparator (VRD-bortezomib-lenalidomide-dexamethasone), this median PFS benefit has narrowed to just 14 months (50 vs. 36 months).[9] There is no reason to believe the benefits would be different in other parts of the world. However, what level of TRM justifies this narrow PFS benefit needs to be addressed.

The STUR have not gone up proportionately in the rest of the resource-challenged regions (1.8–4%).[2] The common reasons for these are financial limitations, patient perception, and cultural bias.[10] This is despite Indian patients with myeloma being younger and having a high-risk disease at onset.[11] The ASCT TRM in most Indian centers is still high (2–7.2%).[12] Possible reasons for this include the frailty of Indian patients at the time of ASCT with increased toxicity from ASCT and center experience.[13] A systematic review and meta-analysis done in the era of such high TRM in the resource-rich settings[14] found that the odds ratio of TRM was three times with upfront ASCT compared with SDT (~2%). The calculated number needed for treatment harm from upfront ASCT was 26. This number was high enough to question the benefit of ASCT in favor of alternative treatment options. It took the resource-rich settings more than two decades to decrease the TRM to just approximately 1%, which brings the number needed for treatment harm to more than 100, justifying frontline use of ASCT in all eligible patients. As centers expand their ASCT numbers, their TRM rates will naturally decrease with experience and better supportive care.[1,14] Until then, centers in resource-challenged settings should periodically audit their TRM from SDT and ASCT and make an informed decision by discussing the pros and cons of upfront ASCT in consultation with their patients. Without a substantial survival benefit, even quality of life benefit will help guide the patient's decisions until the TRM rates are down to 1% or lower.[10]

Conflicts of Interest
None declared.

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article published online
December 3, 2022

DOI https://doi.org/10.1055/s-0042-1754373.
ISSN 0971-5851.

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The Care of Childhood Cancer Survivors in India: Challenges and Solutions

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Ind J Med Paediatr Oncol 2024;45:167–172.

Abstract

Purpose We describe the challenges faced and lessons learnt over three decades of a childhood cancer survivorship program in India.

Methods We provide a descriptive analysis of the challenges and barriers faced in running this program, our strategies in management, and detail the stages of development of holistic support system.

Results The profile of late effects in our cohort of survivors is notable for the high prevalence of psychosocial issues and metabolic syndrome. Major difficulties faced were transitioning of patients to survivorship care and attrition to follow-up, which were overcome to an extent by ensuring constant communication/rapport-building, updated databases, and peer support groups. Collaborations with nonprofit organizations and other donors have enabled financial, psychosocial, educational, and vocational rehabilitation.

Conclusions It is feasible to establish and sustain a survivorship program in a large-volume center in low- and medium-income country. Understanding the unique spectrum of late effects and establishing a holistic support system go a long way in ensuring the long-term physical and mental health and psychosocial concerns of childhood cancer survivors. Decentralization, development of a strong national networks, capacity building, and incorporation of sustainable technology should be priorities in survivorship care.

Keywords
- childhood cancer survivors
- low- and middle-income countries
- survivorship care

Key Points

In this manuscript, we describe the lessons learnt over three decades of a late effects program in India. We also describe our strategies of transitioning to survivorship care and tackling attrition to follow-up. We have found that constant communication/rapport-building, updated databases, and peer support groups have helped tackle the problems of attrition. Collaborations with nonprofit organizations and other donors have enabled financial, psychosocial, educational, and vocational rehabilitation. It is feasible to establish and sustain a survivorship program in low- and medium-income countries (LMICs). Understanding the unique

article published online
April 17, 2023

DOI https://doi.org/10.1055/s-0043-1761262.
ISSN 0971-5851.

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

spectrum of late effects and holistic support goes a long way in ensuring the long-term physical and mental health and psychosocial concerns of childhood cancer.

Introduction

Survivors of childhood cancer are at risk of developing long-term health conditions; the prevalence increases with time and aging, necessitating lifelong care.[1–3] However, survivorship care has been a relatively underserved area in India, and the increasing interest in survivorship care in India over the past few years has been limited to the larger centers.[4]

As the oldest and largest survivorship clinic in India, the After Completion of Treatment (ACT Clinic at Tata Memorial Hospital, Mumbai) has successfully established and expanded a late effects program within a high-volume pediatric oncology unit.[5–7] All survivors are seen by pediatric oncologist and psychologist, and selected survivors are assessed by radiation oncologists, surgical oncologists, dietician and social worker, cardio-oncology, and endocrinology clinics, as required.[8,9] The ACT Clinic coordinates the care of over 3,600 long-term survivors of childhood cancer from all regions across India. The ACT Clinic has been instrumental in mentoring several Indian centers in starting late effects services, and we feel that the lessons learnt over the last three decades would be of use to all those interested in establishing their own survivorship program. The ACT Clinic can be a successful model that can be replicated in similar settings. The stages of development of the ACT Clinic as well as the burden of late effects in childhood cancer survivors (CCS) registered at our clinic have been published during the initial years as well as recently.[5–7] We describe below some of challenges that we faced, feasible solutions, and lessons learnt by us during the past three decades.

The Need to Recognize the Unique Spectrum of Late Effects in India

An increasing body of literature suggests that survivors of childhood cancer are more likely than their siblings to develop long-term effects of cancer, with the disparity becoming more evident with increasing age.[1–3] In one of the largest cohorts of adult survivors of CCS, the most prevalent clinically ascertained adverse outcomes were pulmonary (65.2%), auditory (62.1%), endocrine or reproductive (62.0%), cardiac (56.4%), and neurocognitive (48%).[3]

The prevalence and spectrum of late effects in our cohort have been published.[5–7] The high prevalence of transfusion-transmitted viral infections and metabolic syndrome or its components have been noted from several centers in India.[4,7–10] Psychosocial issues (including scholastic issues and school dropouts) are multifactorial and need holistic and consistent assessment and interventions.[7,11] Survivors of certain cancers—retinoblastoma, brain tumor, and nasopharyngeal carcinoma—who had the highest cumulative incidence of chronic and disabling late effects need special attention and multidisciplinary monitoring and rehabilitation.[7] However, a national survey to assess delivery of services to CCS found poor availability of extended service providers such as endocrinologists and psychologists.[12]

Transitioning from Acute Care to Survivorship Care: Catch them Early, and Catch them Young

One of the major challenges that we have faced is to streamline and increase recruitment to the ACT Clinic in our high-volume center. Children who complete treatment are followed up in the routine outpatient department until they are eligible to enroll in the ACT Clinic, that is, 5 years from start of treatment and 2 years from completion of treatment. Care of the survivors is then continued in the ACT Clinic. Of eligible survivors who initiated anticancer treatment between 2010 to 2012 and 2013 to 2016, only 65 and 53% (respectively) have transitioned to long-term care. Large numbers (600–1000 patients completing treatment/year) of patients and limited days of ACT Clinic functioning (2 days/week) necessitate additional stay for patient contribute to this discrepancy.

Another concerning finding was that at entry to the survivorship care, several children have scholastic and health issues (including overweight in 10% of child/adolescent survivors) unaddressed during routine outpatient visits, or have not been reimmunized as advised.[8,9] Additionally, certain "late" effects, such as endocrinopathies in survivors of brain tumors, may start during or soon after treatment, which necessitates special care.[13]

To avoid missing on such crucial, preventable, and actionable issues, we have started the "Early Reintegration Program," which focuses on the transitional period between completion of treatment and survivorship care. Children are screened by a team of nurse, dietician and psychologist for growth, scholastic and adjustment issues, and advised regarding healthy lifestyle, the need for disciplined follow-up and reimmunization. This screening is done on the same day as scheduled outpatient clinic visit. Children with concerns picked up on screening receive detailed evaluation and intervention by specialists.

The C2S study, under the aegis of Indian Pediatric Oncology Group (InPHOG), a multicenter registry of children completing cancer treatment—which attempts to streamline the process of transition to survivorship care—is a welcome step in this direction.[14]

Tackling the Problem of Attrition to Follow-Up, Especially in Adult and High-Risk Survivors

Attrition to follow-up with passing time continues to be a major cause for concern at our clinic. Of 3,067 survivors, 720 (22.5%) have not returned for follow-up at the ACT Clinic for 5 years or more.[7] Expectedly, a far higher proportion of survivors (60% of survivors treated prior to 2000) from the earlier decades are lost to follow-up. Analysis of our cohort also showed that 36% of survivors treated prior 2000 had a late effect requiring intervention (grade 2 and higher) compared with 16.2% treated after 2000.[7] This phenomenon has been noted world-over.[2,15] A recent audit at our clinic found that the major causes for attrition to follow-up include gaps in awareness, financial toxicity, and "social stigma," similar

to results of a nationwide survey.[12,16] At registration into the ACT Clinic, the gender ratio of 2.5:1 (male preponderant), while skewed, was similar to that at initial cancer diagnosis at our center. However, several female survivors discontinue clinic visits into adulthood and marriage. Societal pressures, often gendered, significantly influence health-seeking behaviors across the cancer continuum in India, and are challenging to overcome.[17]

Our approach to tacking this has been multipronged:

a) Repeated reinforcement by the pediatric oncologists and psychologists in ACT Clinic at each visit regarding long-term follow-up. There is emphasis on "high-risk" survivors, specifically older survivors, those with pre-existing health concerns and those with treatment exposure likely to necessitate longer and more intensive health monitoring
b) Proactive follow-up: Our clinic policy has been to send out postal letters once every 5 years to the last known postal address of survivors. This is often an exercise in futility due to outdated and incomplete postal addresses for the older patients. Recently, we have started flagging delayed follow-ups in our database and contacting them over telephone and email. Despite the effort involved, even a single response is gratifying in 2020, we contacted 480 and received 45 responses; the median age of these survivors was 28 years with a median lost-to follow-up duration of 8 years.
c) Updated contact information: At each follow-up visit, the contact information (at least 2 telephone numbers, email and postal address) of all survivors are updated in the ACT Clinic Database. Survivors are provided the corresponding contact information of ACT Clinic at each follow-up and actively encouraged to keep in touch by email, telephone or WhatsApp.
d) Establishment of a holistic support model (described below).

Attrition to follow-up has definitely decreased over the last two decades, with only 2% of survivors diagnosed after 2010 being lost-to follow-up, and will hopefully become negligible in the future.

The Importance of Holistic Support

Financial hardship in long-term survivors of childhood cancer is being increasingly recognized, especially in those with chronic late effects.[18,19] State schemes may cover a substantial part of treatment in children with cancer, but survivors of childhood cancer (CCSs) in countries like India which lack established universal healthcare coverage may incur significant out-of-pocket expenditures. While travel and basic investigations are heavily subsidized and supported by our public funded hospital, survivors need funding for costs of medical treatment, food, lodging, etc. Certain late effects of treatment incur heavy expenditure—the average annual cost of growth hormone treatment is INR 300,000 (USD 4000) and antiviral treatment is INR 30,000 (USD 400) at our center; the per capita income in India is USD 6600 in terms of purchasing power parity, but only close to USD 2200 in actual terms.[20] The expense precluded growth hormone treatment in most patients prior to 2015 since treatment funding is generally available only to patients on active anticancer treatment. Long hospital visits may lead to loss of daily wages for adult survivors and parents of child survivors. Until recently, medical insurance was not available to survivors of cancer in India.

Since 2016, the pediatric foundation—ImPaCCT foundation—at our hospital has been receiving funding specifically for survivors of childhood cancer.[21] From 2016 to 2020, these survivorship funds (totaling INR 56.6 million; USD 6,80,000) have enabled us to support the cost of late effects surveillance and treatment in 450 survivors—including growth hormone supplementation in 100 survivors, second malignancy management in 20 survivors, antivirals therapy in 38 survivors, and other hormonal treatments/ assisted reproduction. The inclusion of in-house cardio-oncology, endocrinology, and hepatitis clinics also helped co-ordinate the management of medical costs and reduce costs, including out-of-pocket expenditure. Funding for education of survivors and patients on maintenance treatment via pediatric foundation, nonprofit organizations and individual donors has immensely benefited our survivors.[4] Multiple nonprofit organizations partner with us to provide medical and vocational rehabilitation. The addition of foundation-employed dietician, nurse, and data manager to our team has led to improved quality of services and streamlined functioning. The evolution of the multidisciplinary, holistic support offered by the ACT Clinic has been described elsewhere.[7]

The holistic care available at our clinic (detailed in ref. [7]), predominantly financial assistance and educational/vocational guidance, has possibly played a part in improved follow-up.

Barriers to Communication and the Need for Rapport Building

The sociocultural barriers to effective education and communication with survivors and families tend to be multiple and complex in India.[22] Overprotective families, lack of autonomy for adolescent and young adult survivors, societal pressures, and taboos surrounding issues such as fertility and sexual health often preclude discussion and effective communication with survivors and families.[23] Thus, awareness and sensitization regarding potential late toxicities are often lacking, and we often need to "start from scratch" when survivors are independent and autonomous adults.

Establishing a strong relationship with constant communication, especially in adolescent/ young adult and aging survivors, is crucial.[24] Patient education should start with newly diagnosed patients with cancer and extend through survivorship, modified to suit individual understanding and adjusted for mental health and cultural preferences. All survivors are seen by either of the two pediatric oncologists at the ACT Clinic, and all older adult survivors are seen by the senior pediatric oncologist and senior psycho-oncologist who are familiar with their medical and psychosocial concerns. This rapport-building has helped immensely in ensuring continuity of care and adherence to follow-up in a large

proportion of survivors, who often refer to the medical team as their extended family.

Ugam—a support group of CCS from ACT Clinic, initiated by the Indian Cancer Society—has been active for over a decade in peer support, empowerment of survivors, and advocacy.[25] The ACT-Ugam model has been successfully replicated by the Indian Cancer Society to provide holistic care to cancer survivors across the country.[26]

Telesurvivorship and Distant Follow-Up are Feasible and Effective

Since 2017, due to the large volumes at our center, we have actively incorporated distant follow-up and shared care; this stood us in good stead during the COVID pandemic. Our strategy during the first 15 months of the COVID pandemic has been described in detail.[27] Analysis of the trends at our center points toward increasing use of telesurvivorship, especially in survivors with no/few late effects, easy access to technology, and stay in places distant from Mumbai.[27] However, in-person follow-ups will continue to remain high, especially in those who stay in Mumbai and surrounding areas, and those with medical/psychosocial concerns who depend on our in-house onco-endocrinology, cardio-oncology and hepatitis services, which offer subsidized care. While the majority of urban survivors have access to WhatsApp and internet, there is a small proportion of survivors who lack access, and an even smaller proportion (mainly rural and semi-literate) who are uncomfortable with distant follow-up. Overall, telesurvivorship has been successful, and multiple modalities may be effective depending on the survivors' access to technology. We actively encourage in-person follow-ups at present.

The Need for Adapted Treatment Guidelines

Current guidelines for the follow-up of survivors originate from large collaborative groups in North America and Europe.[28,29] While these surveillance guidelines are comprehensive, evidence-based and thoroughly scrutinized by experts, their direct application in resource-limited settings might not be feasible or cost-effective. There is very little long-term data that can help direct the specific requirements for CCS from LMICs. Ethnic, racial, cultural, and sociodemographic variations necessitate adaptation of international guidelines to suit local needs.[30]

To decentralize survivorship care, it is essential to have several levels of adapted treatment guidelines which can be used at each level of care. While adapted treatment guidelines and levels of care for various tumor types and supportive care have been laid down by the International Society for Pediatric Oncology, these do not include survivorship.[31] Despite efforts by individual centers and special interest groups among pediatric oncologists in India, there have been no national consensus guidelines for survivorship care till date.

At our center, we ensure risk-stratified and exposure-based screening using an adapted version of standard guidelines that focuses on history, physical examination, basic laboratory investigations, and higher diagnostics used only as indicated.

Future Directions for the ACT Clinic and Survivorship Care in India

a) Decentralization of care and capacity building: Decentralization of care, with a shift toward shared-care and remote follow-up, especially in low-risk survivors, is a main priority for us, especially considering our large patient volume of diverse geographical origin. This could be facilitated by the development of a strong multicentric network of late effects clinics providing holistic, standardized care as well as a network of support groups/supportive care services. Successful efforts in this direction are already being spearheaded by nonprofit organizations, namely Cankids Survivor Passport2Life clinics and Project PICASSO of the Indian Cancer Society.[4,26]

b) Incorporation of technology: With over 50% of our survivors being adolescent and young adults—who are internet-savvy—technology can be leveraged in multiple ways to greatly expand the scope of survivorship care. Internet-based, individualized survivorship care plans that may be accessed securely by the survivor or local designated physicians can help effective decentralization of care.

   Several ongoing interventions—psychosocial, cardiometabolic health, educational—can be sustainably performed individually or in groups via videocalls. The existing online support groups can be expanded to include all categories of survivors as well as parents and caregivers. The past few months have greatly improved our capabilities of online communication and greatly broadened the scope of digital interventions.[32]

c) Education: There is a definite need for improved education and sensitization of patients/survivors, families, and healthcare professionals regarding potential late toxicities. There should be an increased focus on minimizing avoidable late toxicities and adopting best practices in treatment. Pediatric oncologists need to be sensitized toward simple interventions such as semen cryopreservation and monitoring for cardiac and ototoxicity during treatment.

d) Research: A strong understanding of the profile of late effects and other concerns faced by survivors of childhood cancer is required, both for development of adapted guidelines and for relevant interventions. The projects and collaboration within the multicentric Late Effects subcommittee of the InPHOG[33] are a welcome step in this direction. However, interventional research relevant to our population needs to be the priority focus. While there have been several attempts to minimize neurocognitive issues and azoospermia, late effects amenable to intervention like cardiometabolic complications, frailty and psychosocial toxicities are other areas in urgent need of pre-emptive and innovative solutions.[34–37]

Funding
None declared.

Conflict of Interest
None declared.

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Enhancing Logistic Support During Chemotherapy to Nonlocal Children with Cancer and Their Families through Home Away from Home Program

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Ind J Med Paediatr Oncol 2024;45:173–175.

Abstract

Childhood cancers have excellent outcomes in terms of cure rates and survival if they are diagnosed early and treated appropriately. However, there is a huge disparity in outcomes between high- and low-middle income country(ies) due to out-of-pocket expenditure, therapy abandonment, and severe infections. To bridge these gaps in outcomes, a partnership between a private medical institute and a nongovernmental organization was fostered to develop a long-stay facility for children with cancer and their families while receiving disease-directed therapies. This report aims to expound the story of development of the "Home Away from Home" program and its transformative potential and societal impact.

Keywords
- logistics
- low-middle income country
- pediatric oncology

Background

In the setting of childhood cancers, a disparity in treatment and survival outcomes is noted among high-income countries (HICs) and low-middle-income countries (LMICs), with an 80% and upward long-term survival in HICs and 30 to 40% in LMICs.[1–3] Treatment refusal and abandonment often contribute to this disparity, along with delayed presentation, severe infections, and poor nutrition.[4,5] Out-of-pocket spending, high cost of cancer therapies, and nonaffordability often lead to decisions surrounding treatment refusal and abandonment.[4,6] Direct costs corresponding to their cancer therapy are often supported by government or private insurance or bridged through external funding.[4] However, during prolonged cancer therapy, indirect costs toward logistics such as housing, food, and travel, especially for families nonlocal to the cancer center, can be daunting, often leading to treatment abandonment.[4,5] A Home Away from Home program was an initiative to mitigate this treatment abandonment by enhancing logistic support during chemotherapy for children with cancer and their families.

An audit of our childhood cancer services showed that 5% of the treatment abandonment among nonlocal families was due to indirect costs associated with treatment logistics.[7] Despite receiving adequate financial help toward cancer-directed therapies, the mounting indirect costs hindered their continuation in the cancer center. Most children with treatment interruptions or abandonment had cancers that had excellent potential for cure. Furthermore, families

article published online
September 22, 2023

DOI https://doi.org/10.1055/s-0043-1771022.
ISSN 0971-5851.

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

Table 1 Timelines for the development of the home away from home

Process	March 2021	April 2021	September 2021	October 2021	November 2021	March 2022	April 2022
Initial communication and Zoom discussion							
Discussion with hospital and university administration							
Visit by the NGO and identification of premise							
Preparation and signing of the memorandum of understanding							
Starting of the renovation work							
Completion of the renovation work							
Operational start of the center							

continuing treatment also experienced significant distress related to financial toxicity. The expenses were mainly due to rentals, food, local travel, and child needs. These children's rental accommodations were small units, often unclean, and unsuitable for a child's stay. It was seldom a homelike environment and deprived the child of education and entertainment. Besides, we as a service endeavor that no child should be denied cancer treatment due to lack of funds. Thus, we explored the possibility of creating a system to mitigate these concerns.

Conceptualization, Collaboration, and Co-Creation

A nongovernmental organization (NGO), Access Life Assistance Foundation (AL),[8] was approached to replicate the respite and long-stay models that they had built in Indian cities like Pune and Mumbai to support children with cancer. AL is a nonprofit organization that started in 2014. It provides accommodation with hygienic and quality living environment for the children with cancer and their parents with no cost to them. A memorandum of understanding was signed between two partnering organizations. Both partnering organizations agreed to share costs involved in setting up the center and maintaining it. AL did a feasibility assessment and visited the premises to understand the local needs. Subsequently, they offered to support the capital and operational costs of the new center at Manipal, India. Over the next few weeks, an area closer to the pediatric oncology clinical services was identified to minimize transport costs. The timelines are provided in ►**Table 1**.

The center is built over 9,000 ft^2 and the facility is wheelchair accessible. It is Wi-Fi enabled and has a security surveillance system. The amenities at the center and their description are provided in ►**Table 2**.

Operations

Every family that moves into the center is provided with a kit that enables them to sustain their stay at the center. The kits include utensils like plates, spoons, steel tumblers, pressure cookers, and other steel utensils essential for cooking, and hygiene kits that include soap, hand sanitizer, nail clippers, hot flask, medicine box, dental hygiene kit, comb, and spirometer.

All patients seeking admission at the center are assessed by the hospital medical social worker to determine their eligibility based on the strict assessment criteria. The assessment criteria include parameters like socioeconomic status along with details like possession of land, vehicles, etc., distance from

Table 2 Amenities within the center

Sl no.	Room description	Approximate area available (ft^2)	Main function
1	Recreational area	800	Indoor recreational activity
2	Kitchen area	88	Cooking
3	Dining area	120	Meal time
4	Counseling room	110	Psychosocial counselling
5	Center coordinators room	110	For the center coordinator to stay
6	Office area	110	For administrative work
7	Family units	480 (40 × 12 units)	For families to sleep
8	Washrooms and toilets	400	Washrooms
9	Outdoor play area	2,800	Recreation and games
10	Outdoor garden	2,800	Kitchen garden and relaxation

the cancer center, and availability of a unit to stay. The social worker will liaise with the center manager to complete the admission process and allotments of the family units based on availability. The allotment of unit is on a first come first served basis and patients who need the facility after the facility is full is waitlisted and allotted as per the waitlist. Furthermore, the children and families are able to access an array of support services at the center, which include hygienic accommodation, psychosocial support, vocational training, nonformal education, and recreational activities.

The center coordinator ensures that the families have a pleasant stay and receive all the care needed, oversees the efficient management of the center, and handles the documentation, case studies, and interactions with funders. The operations manager, human resource department, finance, and administrative team from the head office at Mumbai, India offer technical and logistic support remotely and through periodic visits to the center.

Evaluation of the Impact of the Center

Various key performance indicators are assessed annually to understand the impact of the center. Few of the indicators include the following:

- Reduction in treatment abandonment rate.
- Reduction in out-of-pocket expenditure in those staying at the center versus those staying outside the center.
- Reduction in mortality during intensive therapy in those staying at the center versus those staying outside the center.
- Quality-of-life studies for children and caregivers.

Reduction in treatment abandonment rate has been the vital key performance indicator. In a retrospective audit, the treatment abandonment rate in the division was 4.5%, which had reduced to 0 when looked at 8 months after the intervention.[7] Twenty-eight children and 56 caregivers benefitted within a span of 8 months of initiation of the Home Away from Home program.

Conclusion

Although in India there are some "Home Away from Home" centers set up alongside tertiary cancer care centers treating children with cancer, it was always with a public health institute partnering with an NGO. It is the first project where an NGO has engaged with a private medical institute for developing a pediatric oncology respite and long-stay facility. Furthermore, this project resonates with the theme of international childhood cancer day 2022, where better survival is achievable through your hands. In this project, multiple hands worked synchronously and collaboratively for the benefit of children with cancer and their caregivers. Creating facilities like these helps in capacity-building in comprehensive pediatric cancer cares that complements the treatment with a safe, secure, nourishing, and positive environment. It endeavors to enhance the cure rate and survival rate by reducing costs, minimizing treatment abandonment, improving compliance, and limiting infections. We hope to develop this as an emancipatory transformative model that could be scalable and replicable and provide a platform to create funding opportunities for childhood cancer.

Author Contributions

Vasudeva Bhat K., Naveen S. Salins, and Sharath Kumar Rao conceptualized the center and the manuscript. Ankeet Dave and Girish Nair did the planning of the center and contributed to the manuscript. Archana M.V., Krithika Shantanu Rao, and Vinay M.V. drafted the manuscript with provision of intellectual content.

Funding

The budget for the facility is divided into the capital budget and operational budget. The capital budget was achieved through corporate social responsibility of multinational companies, local foundations, philanthropic support, and individual donors. The operational budget for the center was managed by an alumnus of the Manipal Academy of Higher Education for a duration of 5 years.

Competing Interests

None declared.

Acknowledgments

The authors acknowledge the individual donors and corporates toward their support in construction and operational expenditures. The authors also acknowledge other resource personnel of the Manipal Academy of Higher Education as well as Access Life Assistance Foundation for their valuable contributions.

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Pharmacoeconomic Analysis of Treating Lung Cancer with Different Regimens Using the Cheapest and Costliest Brand and the Generic Jan Aushadhi Drugs Marketed in India

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Ind J Med Paediatr Oncol 2024;45:176–182.

Abstract

Background/Purpose of the Study The costs of chemotherapy drugs which are vital in the treatment of lung cancer can be exorbitant. The current study was undertaken to ascertain cost minimization analysis by comparing costliest and cheapest branded with Jan Aushadhi (JA) drugs marketed in India.

Methods The cost of costliest, cheapest branded, and JA drugs were collected from the designated reference sites. The cost difference, cost ratio, and percentage of cost variation were calculated as per cost minimization study guidelines.

Results The results of the analysis suggest that the JA drugs were much cheaper than the branded drugs and when used in regimens resulted in substantial cost savings. The biggest financial advantage was seen in the commonly used cisplatin–pemetrexed regimen where cost saving of Rs. 268,002 was observed for the whole treatment of six cycles. Using JA drugs also reduced the cost for the targeted therapy with gefitinib and erlotinib.

Conclusion The cost minimization study, which is the first in this field of lung cancer, clearly indicates the usefulness of JA drugs in reducing financial costs for the patient.

Keywords
- lung cancer
- anticancer drugs
- pharmacoeconomics
- Jan Aushadhi
- cost difference
- cost ratio
- percentage of cost variation

Introduction

Chemotherapy is important in lung cancer treatment, and depending on the stage, it is used either as the only modality or before or after surgery or radiation.[1] However, chemotherapy costs patient substantially and liquidates their lifelong earnings/savings. In hospital pharmacy, cost minimization analysis (CMA) is important aspect and attempts at understanding the financial impact of drug costs on the patient considering different marketed brands. The Government of India has initiated Jan Aushadhi (JA) outlets across the country where generic drugs are available at reduced price and has been immensely useful for the poor.[2] The current study compared the CMA taking into account the most expensive and least expensive branded anticancer drugs with the JA drugs. By assessing the economics of chemotherapy drugs, the

article published online
March 14, 2024

DOI https://doi.org/10.1055/s-0044-1779721.
ISSN 0971-5851.

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

study aims to provide insights into optimizing health care budgets and promoting the adoption of economically viable treatment options.

Materials and Methods

Inclusion and Exclusion Criteria

The inclusion criteria considered were to include only those drugs and regimens used in the curative or palliative lung cancer treatment, in accordance to National Comprehensive Cancer Network guidelines. The exclusion criteria included all other drugs and regimen used for treating other cancers.

Study Method

This CMA was performed in accordance to the tenets of pharmacy and health economics research guidelines from October to December 2021. The study evaluated the cost disparities between the costliest and cheapest drugs under the premise that all other costs associated with the delivery of treatment remained constant. Costs of the branded anticancer drugs available in India were obtained from the Current Index of Medical Specialties and the Monthly Index of Medical Specialties, India. JA drug costs were ascertained from the booklet available and from the Pharmaceuticals and Medical Devices Bureau of India. Cost difference, cost ratio, and percentage of cost variation were calculated per tablet/capsule/injection as described earlier.[3]

Anticancer drugs have to be strictly administered considering the body surface area (BSA) of the patient. Bearing this in mind, for this study, the dose and the financial cost for treating lung cancer were estimated adopting the recent National Institute of Nutrition, Hyderabad, India details on average height and weight for Indian men and women. The values of 55 kg and 5.3 feet (162 cm) tall for Indian woman and 65 kg and 5.8 feet (177 cm) tall for Indian man were considered.[4] BSA was calculated and observed to be 1.58 for women and 1.78 for men. For carboplatin, which needs to be provided based on the patient's glomerular filtration rate (GFR) and creatinine clearance, the value of 0.7 for creatinine was considered.[5] The cost for both males and females was calculated for the various regimens for one cycle as well as for six cycles and represented in tables. The primary outcome of the study was to evaluate the cost disparities between the costliest and cheapest chemotherapy drugs used in the treatment of lung cancer.

Results

The cost of the individual JA, costly, and cheap branded anticancer drugs marketed in India is presented in ►**Table 1**. The highest cost saving was observed by replacing branded with JA drug for the commonly used cisplatin–pemetrexed regimen, where saving of Rs. 268,002 was observed (►**Tables 2** and **3**). The cost savings for other regimens are presented in ►**Tables 2** and **3** for males

Table 1 Cost of JA, costly, and cheap branded anticancer drugs marketed in India

Generic name (dose) Tablet/strip or mg/vial		Cost of the single tablet/unit in INR		
		JA	Costly	Cheap
Carboplatin Inj. 150 mg/15 mL		375.00	1,485.00	678.07
Carboplatin Inj. 450 mg/45 mL		1,707.00	3,795.00	2,330.00
Cisplatin	Inj. 50 mg/50 mL vial	156.00	635.00	309.52.00
	Inj. 10 mg/vial	32.00	192.00	63.09
Docetaxel	Inj. 20 mg/mL	Not available	6,500.00	765.00
	Inj. 80 mg/2 mL	1,800.00	13,541.70	1,290.00
	Inj. 120 mg/3 mL	2,700.00	19,750.00	2,325.00
Erlotinib tablet 150 mg (10 tablets)		70.00	541.70	3,545.00
Etoposide Inj. 100 mg/5 mL		76.00	196.00	182.00
Gemcitabine	Inj. 1,000 mg/vial	836.00	6,836.00	4,722.13
	Inj. 200 mg/vial	240.00	1,512.00	468.50
Gefitinib tablet 250 mg (10 tablets)		44.00	1,320	127.60
Paclitaxel Inj. 260 mg/43.4 mL		Not available	13,492.5	7,408.00
Paclitaxel Inj. 30 mg/5 mL		Not available	1,909.00	423.00
Paclitaxel Inj. 100 mg/16.7 mL		540.00	8,076.00	3,162.00
Pemetrexed 500 mg		2,310.00	30,000.00	2,442.00
Pemetrexed 100 mg		810.00	5,950.00	880.00
Vinorelbine 50 mg/5 mL		Not available	16,000.00	4,352.5

Abbreviation: JA, Jan Aushadhi.

Table 2 Details of cost per cycle and the whole regimen for different chemotherapy regimens used to treat lung cancers in Indian males

Regimen name Drugs (mg/m^2)	Male	Male per dose			Male total dose calculation			Fold difference			Difference			PCV		
	Dosage required	Cheap	Costly	JA	Cheap	Costly	JA	Costly/ cheap	Costly/ JA	Cheap/ JA	Costly − cheap	Costly − JA	Cheap − JA	Costly − cheap	Costly − JA	Cheap − JA
Weekly cisplatin 40 mg/m² cost for one cycle	71.2	498.52	1,211	252	498.52	1,211	252	2.4	4.8	2	712.5	959	246.5	142.9	380.6	97.8
Final cost (six cycles)					2,991.12	7,266	1,512	2.4	4.8	2	4,274.9	5,754	1,479.1	142.9	380.6	97.8
Weekly carboplatin (AUC 2) for one cycle	220	1,355.14	2,970	750	1,355.14	2,970	750	2.2	4	1.8	1,614.9	2,220	605.1	119.2	296	80.7
Final cost (six cycles					8,130.84	17,820	4,500	2.2	4	1.8	9,689.2	13,320	3,630.8	119.2	296	80.7
Cisplatin–docetaxel **Docetaxel (75 mg/m²) + cisplatin (75 mg/m²)**	133.5	3,090	26,250	3,600	3,090	26,250	3,600	8.5	7.3	0.9	23,160	22,650	−510	749.5	629.2	−14.2
	133.5	928.5	1,905	468	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
Total for one cycle					4,018.5	28,155	4,068	7	6.9	1	24,136.5	24,087	−49.5	600.6	592.1	−1.2
Final cost for six cycles					24,111	168,930	24,408	7	6.9	1	144,819	144,522	−297	600.6	592.1	−1.2
Cisplatin–paclitaxel **Paclitaxel (175 mg/m²) + cisplatin (100 mg/m²)**	311.5	8,254.25	17,311.5	2,160	8,254.25	17,311.5	2,160	2.1	8	3.8	9,057.3	15,151.5	6,094.3	109.7	701.5	282.1
	178	1,238.08	2,540	624	1,238.08	2,540	624	2.1	4.1	2	1,301.9	1,916	614.1	105.2	307.1	98.4
Total for one cycle					9,492.33	19,851.5	2,784	2.1	7.1	3.4	10,359.2	17,067.5	6,708.3	109.1	613.1	241
Final cost six cycles					56,953.98	119,109	16,704	2.1	7.1	3.4	62,155	102,405	40,250	109.1	613.1	241
Paclitaxel carboplatin **Paclitaxel (175 mg/m²) + carboplatin (AUC 6)**	311.5	8,254.25	17,311.5	2,160	8,254.25	17,311.5	2,160	2.1	8	3.8	9,057.3	15,151.5	6,094.3	109.7	701.5	282.1
	650	3,686.14	6,765	2,457	3,686.14	6,765	2,457	1.8	2.8	1.5	3,078.9	4,308	1,229.1	83.5	175.3	50
Total for one cycle					11,940.39	24,076.5	4,617	2	5.2	2.6	12,136.1	19,459.5	7,323.4	101.6	421.5	158.6
Final cost (six cycles)					71,642.34	144,459	27,702	2	5.2	2.6	72,816.7	116,757	43,940.3	101.6	421.5	158.6
Gemcitabine–cisplatin **Cisplatin (80 mg/m²) + gemcitabine (1,000 mg/m²)**	142.4	928.5	1,905	468	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
	1,780	6,596.13	12,884	1,796	6,596.13	12,884	1,796	2	7.2	3.7	6,287.9	11,088	4,800.1	95.3	617.4	267.3
Gemcitabine D1 + D8					13,192.26	25,768	3,592	2	7.2	3.7	12,575.7	22,176	9,600.3	95.3	617.4	267.3
Total for one cycle					14,120.76	27,673	4,060	2	6.8	3.5	13,552.2	23,613	10,060.8	96	581.6	247.8
Final cost (six cycles)					84,724.56	166,038	24,360	2	6.8	3.5	81,313.4	141,678	60,364.6	96	581.6	247.8
Cisplatin–vinorelbine **Cisplatin (100 mg/m²) + vinorelbine (25 mg/m²)**	178	1,238.08	2,540		1,238.08	2,540		2.1	0	0	1,301.9	2,540	1,238.1	105.2	0	0
	44.5	4,352.5	16,000		4,352.5	16,000		3.7	0	0	11,647.5	16,000	4,352.5	267.6	0	0
Vinorelbine D1, 8, 15, 22					17,410	64,000		3.7	0	0	46,590	64,000	17,410	267.6	0	0
Total for one cycle					18,648.08	66,540		3.6	0	0	47,891.9	66,540	18,648.1	256.8	0	0
Final cost for four cycles					74,592.32	266,160		3.6	0	0	191,567.7	266,160	74,592.3	256.8	0	0
Cisplatin–etoposide **Cisplatin (100 mg/m²) + etoposide (100 mg/m²)**	178	1,238.08	2,540	624	1,238.08	2,540	624	2.1	4.1	2	1,301.9	1,916	614.1	105.2	307.1	98.4
	178	394	596	198	394	596	198	1.5	3	2	202	398	196	51.3	201	99
Etoposide D1, 2, 3					1,182	1,788	594	1.5	3	2	606	1,194	588	51.3	201	99
Total for one cycle					2,420.08	4,328	1,218	1.8	3.6	2	1,907.9	3,110	1,202.1	78.8	255.3	98.7
Final cost for four cycles					9,680.32	17,312	4,872	1.8	3.6	2	7,631.7	12,440	4,808.3	78.8	255.3	98.7

Table 2 (*Continued*)

Regimen name Drugs (mg/m²)	Male	Male per dose			Male total dose calculation			Fold difference			Difference			PCV		
	Dosage required	Cheap	Costly	JA	Cheap	Costly	JA	Costly/cheap	Costly/JA	Cheap/JA	Costly – cheap	Costly – JA	Cheap – JA	Costly – cheap	Costly – JA	Cheap – JA
Paclitaxel (175 mg/m²)	311.5	8,254.25	17,311.5	2,160	8,254.25	17,311.5	2,160	2.1	8	3.8	9,057.3	15,151.5	6,094.3	109.7	701.5	282.1
Final cost for six cycles					49,525.5	103,869	12,960	2.1	8	3.8	54,343.5	90,909	36,565.5	109.7	701.5	282.1
Docetaxel (75 mg/m²)	133.5	3,090	26,250	3,600	3,090	26,250	3,600	22,650	−510	23,160	7.3	0.9	8.5	729.2	−14.2	749.5
Final cost for six cycles					18,540	18,540	157,500	21,600	−3,060	138,960	7.3	0.9	8.5	729.2	−14.2	749.5
Gemcitabine (1,000 mg/m²)	1,780	6,596.13	12,884	1,796	6,596.1	12,884	1,796	11,088	4,800.1	6,287.9	7.2	3.7	2	717.4	267.3	95.3
Total for one cycle (D1, 8, 15)					19,788.39	19,788.4	38,652	5,388	14,400.4	18,863.6	7.2	3.7	2	717.4	267.3	95.3
Final cost (six cycles)					118,730.3	118,730	231,912	32,328	86,402.3	113,181.7	7.2	3.7	2	717.4	267.3	95.3
Cisplatin–pemetrexed **Pemetrexed (500 mg/m²) + cisplatin (75 mg/m²)**	890	4,884	4,884	53,800	4,884	47,850	4,620	9.8	10.4	1.1	42,966	43,230	264	879.7	935.7	5.7
	133.5	117.75	928.5	1,905	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
Total for one cycle					5,812.5	49,755	5,088	8.6	9.8	1.1	43,942.5	44,667.0	724.5	756.0	877.9	14.2
Final cost for six cycles					34,875	298,530	30,528	8.6	9.8	1.1	263,655.0	268,002.0	4,347.0	756.0	877.9	14.2

Abbreviations: AUC, area under the curve; D, day; JA, Jan Aushadhi; PCV, percentage of cost variation.

and females, respectively. The CMA conducted for a 1-year course of the targeted therapy drugs gefitinib and erlotinib showed that JA drug resulted in substantial cost savings when compared with its branded counterparts (►**Table 4**).

Discussion

The cost of chemotherapy varies according to the type and stage of lung cancer, and the anticancer drug and the regimen being planned, and imposes severe financial burden on the patients.[6] The results indicate that the costs for drugs with the same strength vary and that generic JA medications are cheaper than the branded drugs (►**Table 1**).[7] In clinics, pemetrexed, which is usually used with cisplatin or carboplatin, is a first-line, maintenance, and second- or third-line treatment for non–small cell lung cancer (NSCLC),[8] and substitution with a JA drug results in a significant cost reduction for both male and female patients (►**Tables 2** and **3**). A substantial saving was also observed in the CMA for cisplatin–etoposide, gemcitabine–cisplatin, and other regimens when JA drugs were used (►**Tables 2** and **3**).

In recent years, inhibiting Epidermal Growth Factor Receptor (EGFR), which is overexpressed in 10 to 15% of NSCLC patients, is observed to be effective, and the drugs erlotinib, gefitinib, afatinib, and osimertinib are reported to be effective.[9,10] Erlotinib and gefitinib work by blocking the EGFR tyrosine kinase domain through competitive linking at the adenosine triphosphate-binding site.[10] The use of JA drugs resulted in significant cost savings for patients. Lung cancer chemotherapy poses a significant financial challenge, particularly in resource-constrained nations such as India. The overall cost encompasses expenses related to drugs, medical equipment, and hospital stays, placing a substantial burden on patients. For individuals grappling with lung cancer, out-of-pocket expenditures manifest at every stage, spanning initial visits to local health facilities to ultimate diagnosis and treatment at tertiary health care centers. The financial strain is evident in expenses incurred for preliminary investigations, diagnostic tests, and the unavoidable costs associated with travel and accommodation during referrals to higher tier health care facilities. To alleviate the financial strain, the widespread establishment of JA stores, particularly in rural areas, holds promise for assisting economically disadvantaged populations. The same could facilitate the realization of reduced drug prices, aligning with the aspiration for more affordable health care. Instituting social safety nets for marginalized communities stands to enhance accessibility to essential and quality pharmaceuticals. Essential improvements in pharmaceutical policies at both national and state levels are imperative to amplify cost-effectiveness, thereby widening public access to chemotherapy medications.

Conclusion

The observations of the study indicate that the prices of treating lung cancer were decreased, when JA anticancer drugs were used. The findings of the study will be of

Table 3 Details of cost per cycle and the whole regimen for different chemotherapy regimens used to treat lung cancers in Indian females

Regimen name Drugs (mg/m^2)	Female	Female per dose			Female total dose calculation			Fold difference			Difference			PCV		
	Dosage required	Cheap	Costly	JA	Cheap	Costly	JA	Costly/ cheap	Costly/JA	Cheap/ JA	Costly – cheap	Costly – JA	Cheap – JA	Costly – cheap	Costly – JA	Cheap – JA
Weekly Cisplatin 40 mg/m^2) cost for one cycle	62.8	435.52	1,019	220	435.52	1,019	220	2.3	4.6	2	583.5	799	215.5	134	363.2	98
Final cost (six cycles)					2,613.12	6,114	1,320	2.3	4.6	2	3,500.9	4,794	1,293.1	134	363.2	98
Weekly carboplatin (AUC 2)	170	1,355.14	2,970	750	1,355.14	2,970	750	2.2	4	1.8	1,614.9	2,220	605.1	119.2	296	80.7
Final cost (six cycles)					8,130.84	17,820	4,500	2.2	4	1.8	9,689.2	13,320	3,630.8	119.2	296	80.7
Cisplatin–docetaxel Docetaxel (75 mg/m^2) + cisplatin (75 mg/m^2)	117.75	2,325	19,750	2,700	2,325	19,750	2,700	8.5	7.3	0.9	17,425	17,050	−375	749.5	631.5	−13.9
	117.75	928.5	1,905	468	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
Total for one cycle					3,253.5	21,655	3,168	6.7	6.8	1	18,401.5	18,487	85.5	565.6	583.6	2.7
Final cost (six cycles)					19,521	129,930	19,008	6.7	6.8	1	110,409	110,922	513	565.6	583.6	2.7
Cisplatin–paclitaxel Paclitaxel (175 mg/m^2) + cisplatin (100 mg/m^2)	274.75	7,831	15,402.5	1,620	7,831	15,402.5	1,620	2	9.5	4.8	7,571.5	13,782.5	6,211	96.7	850.8	383.4
	157	1,238.08	2,540	624	1,238.08	2,540	624	2.1	4.1	2	1,301.9	1,916	614.1	105.2	307.1	98.4
Total for one cycle					9,069.08	17,942.5	2,244	2	8	4	8,873.4	15,698.5	6,825.1	97.8	699.6	304.1
Final cost (six cycles)					54,414.48	107,655	13,464	2	8	4	53,240.5	94,191	40,950.5	97.8	699.6	304.1
Paclitaxel carboplatin Paclitaxel (175 mg/m^2) + carboplatin (AUC 6)	274.75	7,831	15,402.5	1,620	7,831	15,402.5	1,620	2	9.5	4.8	7,571.5	13,782.5	6,211	96.7	850.8	383.4
	515	3,008	5,280	2,082	3,008	5,280	2,082	1.8	2.5	1.4	2,272	3,198	926	75.5	153.6	44.5
Total for one cycle					10,839	20,682.5	3,702	1.9	5.6	2.9	9,843.5	16,980.5	7,137	90.8	458.7	192.8
Cost for six cycles					65,034	124,095	22,212	1.9	5.6	2.9	59,061	101,883	42,822	90.8	458.7	192.8
Gemcitabine–cisplatin Cisplatin (80 mg/m^2) + gemcitabine (1,000 mg/m^2)	125.6	928.5	1,905	468	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
	1,570	6,127.63	11,372	1,556	6,127.63	11,372	1,556	1.9	7.3	3.9	5,244.4	9,816	4,571.6	85.6	630.8	293.8
Gemcitabine D1 + D8					12,255.26	22,744	3,112	1.9	7.3	3.9	10,488.7	19,632	9,143.3	85.6	630.8	293.8
Total for one cycle					13,183.76	24,649	3,580	1.9	6.9	3.7	11,465.2	21,069	9,603.8	87	588.5	268.3
Final cost (six cycles)					79,102.56	147,894	21;480	1.9	6.9	3.7	68,791.4	126,414	57,622.6	87	588.5	268.3
Cisplatin–vinorelbine Cisplatin (100 mg/ m^2) + vinorelbine (25 mg/m^2)	157	1,238.08	2,540		1,238.08	2,540		2.1			1,301.9	2,540	1,238.1	105.2		
	39.25	4,352.5	16,000		4,352.5	16,000		3.7			11,647.5	16,000	4,352.5	267.6		
Vinorelbine D1, 8, 15, 22					17,410	64,000		3.7			46,590	64,000	17,410	267.6		
Total for one cycle					18,648.08	66,540		3.6			47,891.9	66,540	18,648.1	256.8		

Table 3 (*Continued*)

Regimen name Drugs (mg/m^2)	Female	Female per dose			Female total dose calculation			Fold difference			Difference			PCV		
	Dosage required	Cheap	Costly	JA	Cheap	Costly	JA	Costly/ cheap	Costly/JA	Cheap/ JA	Costly – cheap	Costly – JA	Cheap – JA	Costly – cheap	Costly – JA	Cheap – JA
Final cost (one cycles)					74,592.32	266,160		3.6			191,567.7	266,160	74,592.3	256.8		
Cisplatin–etoposide	157	1,238.08	2,540	624	1,238.08	2,540	624	2.1	4.1	2	1,301.9	1,916	614.1	105.2	307.1	98.4
Cisplatin (100 mg/m^2) + etoposide (100 mg/m^2)	157	394	596	198	394	596	198	1.5	3	2	202	398	196	51.3	201	99
Etoposide D1, 2, 3					1,182	1,788	594	1.5	3	2	606	1,194	588	51.3	201	99
Total for one cycle					2,420.08	4,328	1,218	1.8	3.6	2	1,907.9	3,110	1,202.1	78.8	255.3	98.7
Final cost (four cycles)					9,680.32	17,312	4,872	1.8	3.6	2	7,631.7	12,440	4,808.3	78.8	255.3	98.7
Paclitaxel (175 mg/m^2) cost for one cycle	274.75	7,831	15,402.5	1,620	7,831	15,402.5	1,620	2	9.5	4.8	7,571.5	13,782.5	6,211	96.7	850.8	383.4
Final cost for six cycles					46,986	92,415	9,720	2	9.5	4.8	45,429	82,695	37,266	96.7	850.8	383.4
Docetaxel (75 mg/m^2) cost for one cycle	117.75	2,325	19,750	2,700	2,325	19,750	2,700	8.5	7.3	0.9	17,425	17,050	−375	749.5	631.5	−13.9
Final cost (six cycles)					13,950	118,500	16,200	8.5	7.3	0.9	104,550	102,300	−2,250	749.5	631.5	−13.9
Gemcitabine (1,000 mg/m^2)	1,570	6,127.63	11,372	1,556	6,127.63	11,372	1,556	1.9	7.3	3.9	5,244.4	9,816	4,571.6	85.6	630.8	293.8
Total for one cycle (D1, 8, 15)					18,382.89	34,116	4,668	1.9	7.3	3.9	15,733.1	29,448	13,714.9	85.6	630.8	293.8
Final cost (six cycles)					110,297.34	204,696	28,008	1.9	7.3	3.9	94,398.7	176,688	82,289.3	85.6	630.8	293.8
Pemetrexed–cisplatin	785	4,884	47,850	4,620	4,884	47,850	4,620	9.8	10.4	1.1	42,966	43,230	264	879.7	935.7	5.7
Pemetrexed (500 mg/m^2) + cisplatin (75 mg/m^2)	117.75	928.5	1,905	468	928.5	1,905	468	2.1	4.1	2	976.5	1,437	460.5	105.2	307.1	98.4
Total for one cycle					5,812.5	49,755	5,088	8.6	9.8	1.1	43,942.5	44,667	724.5	756	877.9	14.2
Final cost (six cycles)					34,875	298,530	30,528	8.6	9.8	1.1	263,655	268,002	4,347	756	877.9	14.2

Abbreviations: AUC, area under the curve; D, day; JA, Jan Aushadhi; PCV, percentage of cost variation.

Table 4 Details of cost for gefitinib and erlotinib treatment for 1 month and a year using JA, costly, and cheap branded drugs

Regimen name Drugs (mg/m^2)		Male per dose			Male total dose calculation			Fold difference			Difference			PCV		
		Cheap	Costly	JA	Cheap	Costly	JA	Cheap	Costly	JA	Cheap	Costly	JA	Cheap	Costly	JA
Gefitinib tablet (250 mg stat od)	For 1 d	127.6	1,320	44	127.6	1,320	44	10.3	10.3	30	2.9	1,192.4	1,276	83.6	934.5	2,900
	For 1 mo				3,828	39,600	1,320	10.3	30	2.9	35,772	38,280	2,508	934.5	2,900	190
	Final cost for 1 y				45,936	475,200	15,840	10.3	30	2.9	429,264	459,360	30,096	934.5	2,900	190
Erlotinib tablet (100 mg stat od)	For 1 d	541.7	3,545	70	541.7	3,545	70	6.5	6.5	50.6	7.7	3,003.3	3,475	471.7	554.4	4,964.3
	For 1 mo				16,251	106,350	2,100	6.5	50.6	7.7	90,099	104,250	14,151	554.4	4,964.3	673.9
	Final cost for 1 y				195,012	1,276,200	25,200	6.5	50.6	7.7	1,081,188	1,251,000	169,812	554.4	4,964.3	673.9

Abbreviations: JA, Jan Aushadhi; PCV, percentage of cost variation.

tremendous value to the patient population, the health care fraternity, and the society at large.

Ethics

No patient-specific data or information were required for the study focus on the pharmacoeconomics of drug pricing. Cost of data on medications is available in public domain, and the study did not require approval from an Institutional Review Board.

Ethics Committee Approval

Not required.

Source of Funding

None declared.

Conflict of Interest

None declared.

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Sorafenib-Induced Spiny Follicular Hyperkeratosis: A Case Report with Review of Literature

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Ind J Med Paediatr Oncol 2024;45:183–187.

Abstract

Sorafenib is a multikinase inhibitor used in the treatment of various solid tumors. Mucocutaneous adverse events are experienced by 70 to 90% of the patients receiving sorafenib, underscoring the importance of awareness among oncologists and dermatologists. Spiny follicular hyperkeratosis (SFH) is a benign and rarely reported skin reaction linked to sorafenib. It is characterized by flesh-colored or white, follicular hyperkeratotic spicules, preferentially involving the face, scalp, upper trunk, and upper arms. Besides being acknowledged as a paraneoplastic cutaneous manifestation of multiple myeloma, SFH has also been linked to a few diseases and drugs, other than sorafenib. However, the precise etiopathogenesis remains to be elucidated. We report an interesting case of SFH in a 14-year-old child, 1 week following the initiation of sorafenib. Trichodysplasia spinulosa, multiple minute digitate hyperkeratosis, keratosis pilaris, filiform warts, and pityriasis rubra pilaris are morphologically similar conditions that were excluded by clinicopathological correlation. A complete resolution of skin rash following sorafenib dose reduction further reinforced our diagnosis. Our patient also developed hand-foot skin reaction, facial erythema, and eruptive nevi during treatment. The regrowth of curly hair following chemotherapy-induced anagen effluvium was an interesting development in our case. We report this case to familiarize clinicians with this rare entity.

Keywords
- adverse events
- sorafenib
- spiny follicular hyperkeratosis

Introduction

Sorafenib is an oral small molecule multikinase inhibitor used in the treatment of various solid tumors.[1,2] Its wide usage has led to the identification and reporting of several adverse events (AE), and a better comprehension of its pathophysiology and management. Spiny follicular hyperkeratosis (SFH) is one such benign cutaneous AE with unique clinicopathological attributes, rarely reported following sorafenib treatment.[3–5] We report a case of SFH in a young girl, 1 week following initiation of sorafenib, that subsequently improved on dose reduction.

Case Report

A 14-year-old girl with right side neck swelling of 6-month duration and radiating pain in her right arm for a year was found to have a large cervicothoracic mass encasing the brachial plexus, brachiocephalic, and subclavian vessels and compressing the trachea on magnetic resonance imaging.

article published online
May 12, 2023

DOI https://doi.org/10.1055/s-0043-1766136.
ISSN 0971-5851.

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

Histopathological examination of tissue from the mass established the diagnosis of desmoid fibromatosis. After completing 4 cycles of chemotherapy with adriamycin and dacarbazine, she was initiated on sorafenib (300mg) and celecoxib, a month before presenting to us. Symptomatically, there was considerable reduction in neck swelling and pain. One week following initiation of sorafenib, she noticed progressive dryness and scaling of skin over the head and neck region along with redness and mild pain over palms and soles. She also reported diffuse hair loss of the scalp following chemotherapy before sorafenib initiation. She is the only child of nonconsanguineous parents, with normal psychomotor development, and was fully vaccinated. There was no relevant past or family history.

On examination, there were sheets of skin-colored to whitish, pin-point, spiny, follicular papules involving the head and neck region, with marked involvement of eyebrows, scalp, and ears (►**Fig. 1A–C**). There were short regrowing hairs over the scalp.

Histopathological examination of the papules revealed orthokeratotic follicular plug, mild superficial dermal edema, perivascular, and focal perifollicular lymphohistiocytic infiltrate. The rest of the epidermis, deep dermis, and subcutis were unremarkable (►**Fig. 2**). The clinicopathological correlation and literature search rendered the diagnosis of sorafenib-induced SFH and grade 1 hand-foot skin reaction (HFSR).

Considering the good clinical response to treatment, the dose of sorafenib was reduced to 200mg/day and celecoxib was continued. We prescribed topical keratolytic agents (sulfur-salicylic paste and cream containing 10% urea, and 15% glycolic acid) and ciclopirox containing shampoo for SFH and emollients for hands and feet.

Six months later, on examination, there were no signs of SFH (►**Fig. 1D–F**). However, she complained of tender yellowish thickening of skin over pressure points of soles (►**Fig. 1G, H**), fissured scaly plaques over first finger web space bilaterally (►**Fig. 1I**), multiple acquired melanocytic

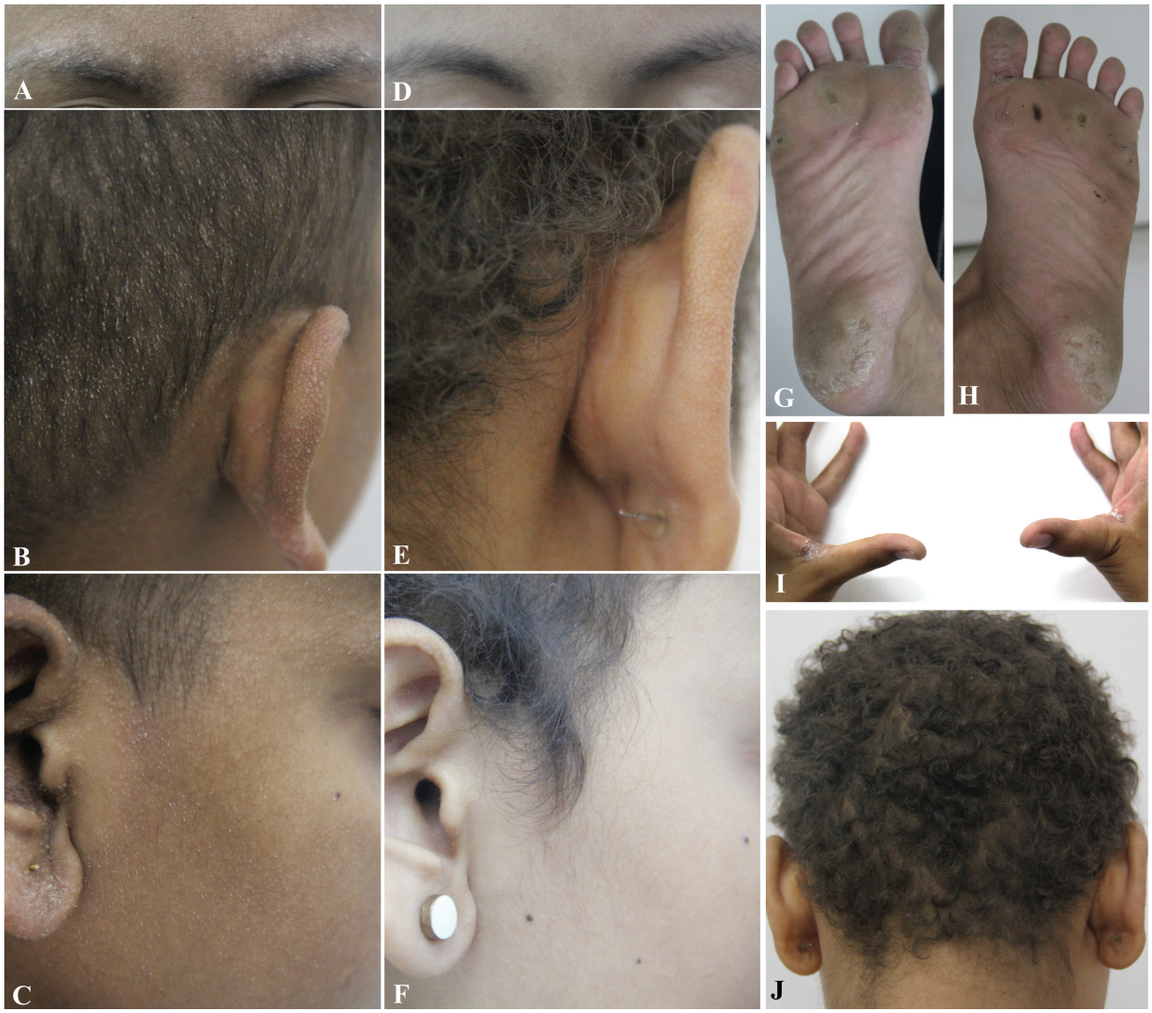

Fig. 1 Skin-colored to whitish, pin-point, spiny follicular hyperkeratotic papules over the (**A**) eyebrows, (**B**) scalp, and (**C**) ears; (**D, E, F**) Complete clearance of rash following sorafenib dose reduction and topical keratolytic application; (**G, H**) Hyperkeratotic hand-foot skin reaction involving the pressure points of soles; (**I**) Fissured scaly plaques over first finger web space bilaterally; (**J**) Regrowth of curly hair following chemotherapy induced anagen effluvium.

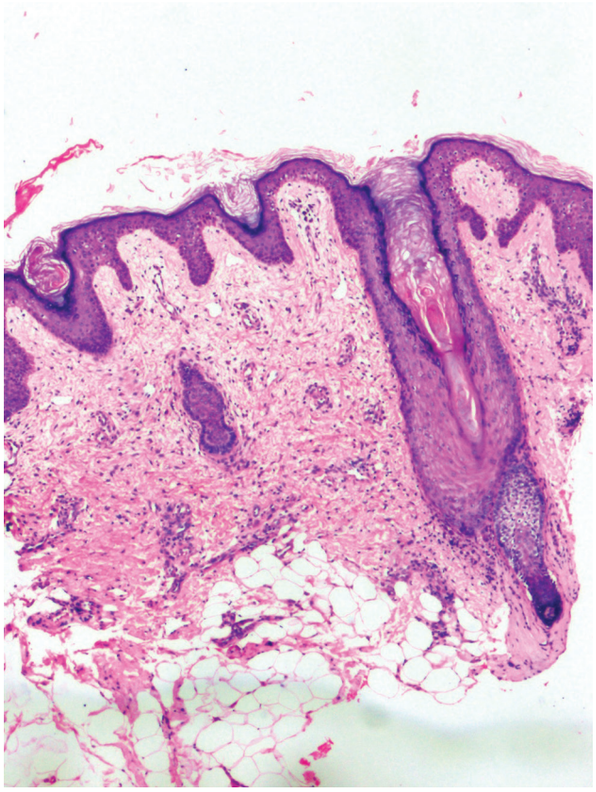

Fig. 2 Orthokeratotic follicular plug, mild superficial dermal edema, perivascular and focal perifollicular lymphohistiocytic infiltrate (hematoxylin and eosin x 100).

nevi on face and neck, and mild erythema over forehead and cheeks. Progression to grade 2 HFSR despite dose reduction and 7 months into treatment was unexpected and unusual. Although neither the child nor her family members had curly hair, the hair that regrew following chemotherapy-induced anagen effluvium appeared curly (►**Fig. 1J**) with reduced pigmentation. The dose of sorafenib was further reduced to 100 mg/day, celecoxib was continued, and mometasone ointment with emollients and cold compresses was advised for HFSR.

The clinical appearance of spiny follicular papules, particularly in the background of malignancy, chemotherapy, and immunosuppression, made us consider different possibilities including viral infections and cutaneous AE of sorafenib. However, histology, together with clinicopathological correlation, and the remarkable response to sorafenib dose reduction and topical keratolytic agents, helped establish the diagnosis.

Discussion

Sorafenib is a multitargeted protein kinase inhibitor that suppresses tumor proliferation (Raf serine/threonine kinases, Fms-like tyrosine kinase-3 or FLT-3, c-Kit, rearranged during transfection or RET blocker) and angiogenesis (vascular endothelial growth factor receptor or VEGFR-2, VEGFR-3, platelet-derived growth factor receptor or PGDF-R-β blocker).[1,3,6,7] In addition to its approved indications, that is, advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and recurrent or metastatic differentiated thyroid carcinoma, it is used off-label in various malignancies.[6,8–10] Approximately 70 to 90% of these patients manifest mucocutaneous AE with hair and nail changes, within 6 weeks of receiving treatment.[1,2,6,7,10,11] HFSR, rash and desquamation, alopecia, facial erythema, subungual splinter hemorrhages, scalp dysesthesias, xerosis, and pruritus are frequently reported; whereas, stomatitis and cheilitis, hyperkeratosis of nipples, eruptive cysts, eruptive nevi, squamoproliferative lesions like actinic keratoses, keratoacanthomas, and squamous cell carcinomas are rarely seen.[1,6–8,11] They may be self-limiting or can persist during treatment. Depending on its type and severity, the AE is managed symptomatically, by dose reduction, treatment interruption, or discontinuation.[1,11]

SFH is one such rare and peculiar dermatological disorder, first identified by Joncas et al and Lopez et al, and later reported by Franck et al, in 21% of patients receiving sorafenib.[3–5] It is characterized by flesh-colored or white, follicular hyperkeratotic spicules, preferentially involving the face, scalp, upper trunk, and upper arms.[5,6,12] It is asymptomatic, devoid of erythema, and appeared 9 to 164 days after treatment initiation in the patient cohort described by Franck et al.[5] Though our patient had a morphologically identical presentation, she exhibited a shorter time-to-onset of SFH, that is, 7 days, and sparing of upper trunk and arms. Follicular dilatation with hyperkeratotic follicular plug and perifollicular lymphocytic infiltrate are the histopathological attributes shared by all SFH cases, including ours.[3–5,12–16] The orthokeratotic digitate spike protruding above the epidermis, a distinct feature demonstrated in one out of the four cases evaluated by Franck et al, was probably lost in the tissue processing of our case.[5]

Trichodysplasia spinulosa, multiple minute digitate hyperkeratosis (MMDH), keratosis pilaris (KP), filiform warts, and pityriasis rubra pilaris (PRP) were the differential diagnoses, excluded based on clinicopathological findings. Trichodysplasia spinulosa is a trichodysplasia spinulosa-associated polyomavirus infection of inner root sheath (IRS) in immunosuppressed individuals, presenting as erythematous to skin-colored papules with folliculocentric keratotic spines on central face and ears, alopecia, and skin thickening, progressing to leonine appearance.[6,17–19] Follicular dilatation with plugging and eosinophilic keratinocytes of dystrophic IRS, containing large trichohyaline granules, are seen in histology; the virus can be identified by electron microscopy, immunofluorescence, and molecular techniques.[6,18,19] MMDH, a rare keratinization disorder, is a morphologically similar entity that is differentiated by its nonfollicular nature, appreciated both clinically and histologically, and localization over the trunk and proximal extremities.[17,20] Sorafenib-induced KP-like eruption and PRP-like eruption are infrequently reported folliculocentric skin disease that demonstrates orthokeratotic follicular plug akin to SFH on histology.[21–24] However, the absence of erythematous inflammatory papules (of KP and PRP) and plaques (of PRP) in our patient rendered these diagnoses unlikely.[23,24]

The improvement in rash with treatment interruption, recurrence on treatment resumption, and persistence of rash throughout sorafenib exposure were evident from previous reports.[3–5] Resolution of SFH with dose reduction and topical keratolytic agents in our patient corroborates with it being a direct toxic effect of sorafenib, reminiscent of HFSR. The ubiquitous RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) pathway plays a critical role in epidermal cell proliferation, differentiation, and apoptosis.[1,6,25,26] Therapeutics targeting the normal signaling can lead to dysfunctional keratinization, evident from the wide variety of cutaneous AEs linked to sorafenib.[2,5,6,22] Vemurafenib, a B-RAF inhibitor, is the other targeted antineoplastic agent, linked to two cases of SFH.[12,15] Being the common target of sorafenib and vemurafenib, RAF kinase is probably involved in the pathogenesis of SFH. Interestingly, a reduction in RAF inhibitors-associated cutaneous AE was observed when combined with MEK inhibitors.[11,27] This was evident in a case of vemurafenib-induced SFH that showed substantial improvement on addition of cobimetinib.[12] Hence, the paradoxical activation of the MAPK pathway was proposed as the underlying pathomechanism leading to follicular hyperkeratosis in SFH.

Besides sorafenib, SFH is linked to various diseases, few drugs like vemurafenib, glasdegib, cyclosporine, acitretin, and can also be idiopathic.[12–16,28] Paraproteinemia, particularly multiple myeloma, is the earliest known association and most frequently linked to SFH in literature.[13,28] Other known associations are Crohn's disease, hypovitaminosis A, chronic renal failure, human immunodeficiency virus infection, cryoglobulinemia, Sezary syndrome, and lymphoma.[13,14,28]

Unlike HFSR, SFH is not a dose-limiting AE. Treatment of SFH with topical retinoids, fluocinolone acetonide gel, and 12% lactic acid cream has been tried in the past with little benefit.[14,28] Discontinuation of the causative drug or management of the underlying condition is considered the definitive treatment.[13,28] Among the 11 cases of sorafenib-induced SFH in literature, six patients showed complete clearance of the rash on discontinuing sorafenib, with recurrence seen in three patients on reinstitution of treatment.[3–5] Our patient, however, responded to dose reduction and topical keratolytic agents, with complete resolution noticed in 4 weeks. Franck et al documented clearance of rash over 4 to 168 days, without any specific topical treatment in their patients. However, details about the management of SFH and spontaneous resolution, if any, are not mentioned in their report. Celecoxib was recently found to have a significant effect on the prevention of HFSR and the management of the associated pain.[29] Although SFH is characterized by similar hyperkeratosis, celecoxib is unlikely to demonstrate a similar impact owing to the noninflammatory nature of SFH.

Conclusion

SFH is a rare benign cutaneous AE scarcely reported in association with sorafenib with no reported pediatric cases to our knowledge. We report this case to familiarize clinicians with its unique clinicopathological attributes that distinguish it from trichodysplasia spinulosa, a viral infection managed by reducing immunosuppression or with antiviral agents.[17–19] It is clear from our case that dose reduction with topical keratolytic agents can lead to complete resolution of SFH. Further, alopecia with subsequent growth of curly hair, HFSR, facial erythema, and eruptive nevi were the other sorafenib-triggered cutaneous AE observed in our patient.[1,6,11]

Declaration of Patient Consent

We certify that patient's consent was obtained for publication of her images and other clinical information, in an appropriate consent form. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgment

None declared.

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Renal Cell Carcinoma in the Background of Autosomal Dominant Polycystic Kidney Disease: Report of Two Cases and Review of Literature

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Ind J Med Paediatr Oncol 2024;45:188–193.

Abstract

Patients with autosomal dominant polycystic kidney disease (ADPKD), especially those with renal failure, carry a higher risk of developing renal cell carcinoma (RCC) compared to the general population. Genetic mutations associated with ADPKD are known but a direct link associated with RCC is still controversial. We discuss the clinical course of two such patients. The first patient was diagnosed with ADPKD at the age of 10 years with an unreported tubulocystic RCC focus on his renal biopsy that was picked up on review 16 years later when he presented with vertebral metastases determined to have originated from the RCC. He was doing well on multikinase inhibitors till 4 years of diagnosis with metastatic disease when he succumbed to progressive disease after 3 lines of systemic therapy. The second patient was diagnosed with ADPKD in middle age and papillary RCC 3 years later. Within 3 months of cancer diagnosis, there was progression to metastatic disease and rapid decline despite systemic therapies. We surmise that the diagnosis of RCC may be missed in ADPKD till the advanced stages. Patients with ADPKD should be monitored regularly with imaging and biopsy if needed. Histology may be varied but once diagnosed, systemic therapies may help disease control.

Keywords

- autosomal dominant polycystic kidney disease
- tubulocystic renal cell carcinoma
- papillary renal cell carcinoma
- mTOR inhibitors
- sunitinib

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder linked to mutations of PKD1 (16p) or PKD2 (4q) genes in 85% and 15% patients, respectively, with incidence varying from 1 in 400 to 1 in 1,000.[1] The condition is characterized by multiple renal cysts with or without extrarenal manifestations such as hepatic/pancreatic cysts and vascular abnormalities (intracranial aneurysms, aortic root aneurysms, mitral valve prolapse, etc.), with variable familial expression. Familial involvement and early renal failure are more common with PKD1 mutations.[1,2] As the fluid-filled cysts in ADPKD replace normal renal tissue, progressive loss of renal function leading to chronic kidney disease (CKD) may develop over time.[3] There is more than twofold higher risk of developing renal cell carcinoma (RCC) in patients with ADPKD in large national databases over a 14-year follow-up period.[4] Surgical specimens of ADPKD patients on dialysis showed 5 to 12% harboring RCC.[5,6] A possible direct association of ADPKD with RCC is, however,

article published online
May 4, 2023

DOI https://doi.org/10.1055/s-0043-57268.
ISSN 0971-5851.

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

controversial, and is more often deemed a coincidence except in those with end-stage renal failure where genetic mutations may trigger malignant transformation.[7]

We discuss the clinical course of two patients who presented to us with metastatic RCC with a background of ADPKD.

Case Report

Case 1

A 26 year-old male with past history of bilateral ADPKD diagnosed at the age of 10 years based on renal biopsy and on irregular follow-up with imaging, presented with left-sided abdominal pain, backache, and weight loss for 6 months. Examination revealed both hepatomegaly (15 × 10 cm) and splenomegaly (7 × 6 cm). Positron emission tomography (PET)-computed tomography (CT) demonstrated 18F-fluorodeoxyglucose (FDG) avid mass involving upper pole of left kidney (4.9 × 7.4 × 7.2 cm) with metastatic retroperitoneal lymph nodes, hepatic and D12 vertebral metastases (►**Fig. 1A–E**). Magnetic resonance imaging (MRI) of spine showed a soft tissue mass involving left side of D12 vertebral body with neural foramen narrowing. Biopsy from vertebral lesion suggested metastatic papillary RCC. After review of all blood parameters that returned normal and a discussion with the patient regarding possible treatment options in intermediate risk disease, systemic therapy with sunitinib was initiated. Partial morphologic and metabolic response was observed on interim PET-CT performed after 4 months. A single fraction of palliative radiotherapy (RT; 8 Gy) was delivered when the backache recurred (approximately 9 months after initiating sunitinib). The patient experienced complete response in backache after 4 weeks. He needed evaluation for recurrent episodes of massive ascites causing breathing difficulty after 18 months of initiating sunitinib. Ascitic fluid cytology was consistently negative for malignant cells but showed hypoproteinemia, which was managed conservatively. He received palliative re-irradiation (20 Gy in 5 fractions) to dorsolumbar spine for worsening backache (1 year after initial RT). After being stable clinically and on imaging for 29 months, a follow-up PET-CT showed an increase in size and avidity of liver lesions, although bilateral renal masses did not show any disease progression. Ascites, right pleural effusion, and pericardial effusion were seen (negative for malignancy on cytology). Systemic therapy was changed to axitinib 5 mg twice daily, with symptomatic improvement and partial response at a follow-up of 15 months following initiation of axitinib. Review of renal biopsy (done at 10 years of age) and vertebral biopsy (done at diagnosis of metastatic disease) revealed that both specimens showed tubulocystic RCC (TCRC), a rare variant of RCC (►**Fig. 2**).

After 1 year of stable disease on axitinib, he developed visible and palpable increase in the soft tissue mass on his back at D12 level, but no change in power or sensorium of lower limbs. His Karnofsky Performance Status was 80 with no new symptoms. Repeat PET-CT showed new liver lesions, new retroperitoneal nodes, progression of D12 vertebral lesion with cord compression, and persistent pleural effusion (►**Fig. 1F, G**). Neurosurgical intervention for decompression was sought but not considered due to overall poor prognosis of the disease. Treatment options including immunotherapy and tyrosine kinase inhibitors were discussed, and the patient opted for third-line therapy with cabozantinib 60 mg daily. Palliative radiation therapy (12 Gy in 4 fractions) was given after discussion of risks of demyelination. The

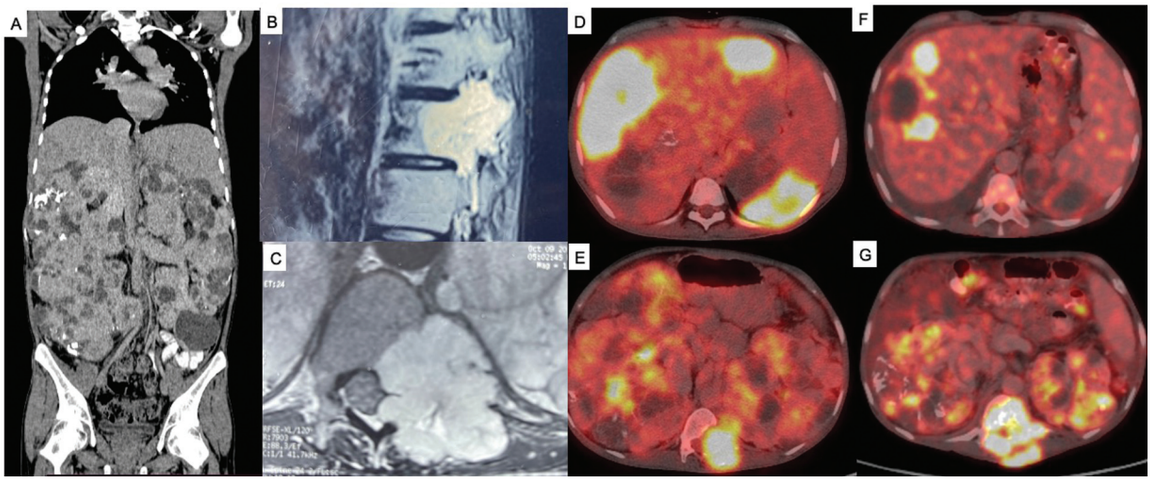

Fig. 1 (**A**) Sagittal section of contrast-enhanced computed tomography (CECT) abdomen showing bilateral polycystic kidneys (Right 26.5 × 14 cm, Left 25.5 × 13 cm) with peripheral and chunky calcification, and multiple liver cysts. (**B**) Sagittal and (**C**) axial sections of magnetic resonance images of dorsolumbar spine showing a large T2 hyperintense lobulated soft tissue metastatic lesion involving D12 vertebra on left side of body, pedicle, and transverse process with involvement of adjacent costovertebral joint, epidural space extension, cord compression, and left neural foramina narrowing at D11-12 and D12-L1 levels. (**D**) Axial sections of corresponding positron emission tomography (PET)-CECT images showing multiple cystic liver metastases with fluorodeoxyglucose (FDG) uptake, largest in right lobe (largest11.2 × 7.3 cm) with peripheral enhancement on arterial phase, and (**E**) multiple bilateral renal cystic masses with soft tissue component and FDG avidity, and left D12 vertebral metastases. (**F**) Axial PET-CECT image on follow-up showing progressive necrotic liver metastases; many new liver lesions had developed (not shown in image), and (**G**) progression in extent of D12 vertebral lesion and soft tissue component with cord compression.

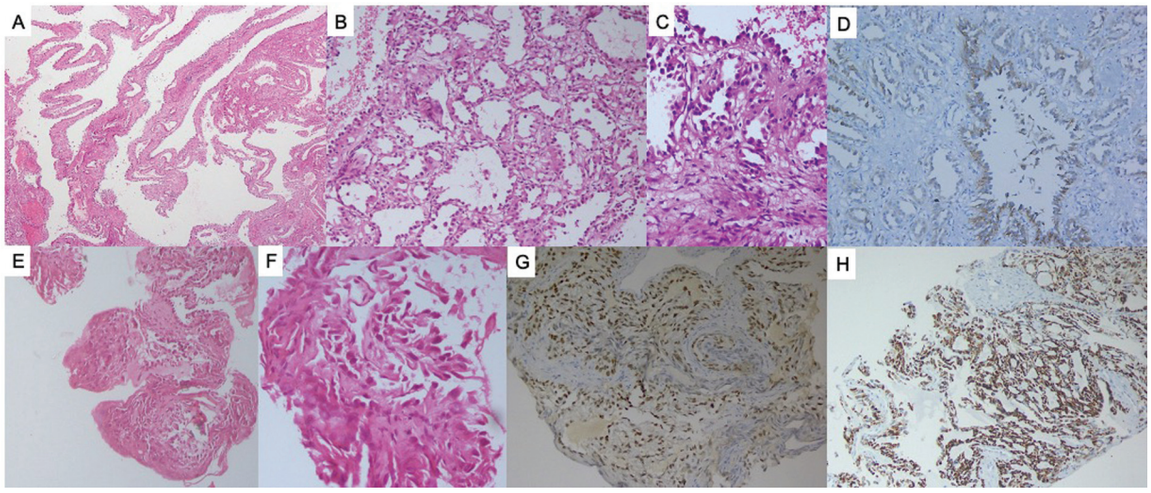

Fig. 2 Renal biopsy specimen obtained at the age of 10 years with a clinical diagnosis of autosomal dominant polycystic kidney disease. (**A**) Low power images of kidney biopsy showing cystic spaces separated by fibrous septae. (**B**) At places they are mixed with closely packed tubules. (**C**) Lining cells are lined by cuboidal cells showing prominent hobnailing with uniform nuclei, minimal atypia, and mitosis. (**D**) These tumor cells are positive for alpha methyacyl CoA racemase (AMACR) immunostains. At the age of 26 years, the patient was evaluated for low backache and biopsy from D12 vertebral soft tissue mass was obtained. (**E**) Small biopsy fragments showing metastatic deposit of tumor with same morphology as renal biopsy taken 16 years ago. (**F**) High power shows hobnailing, with abundant eosinophilic cytoplasm and low atypia and mitosis. (**G**) These cells show nuclear staining for PAX8, and (**H**) cytoplasmic staining for AMACR.

vertebral disease responded to palliative RT and the visible bulge on his back disappeared, but he developed a seizure episode and progressive weakness of lower limbs within 4 weeks of palliative RT. MRI brain ruled out any intracranial cause for the weakness and renal/liver functions and electrolytes were normal. His oral intake progressively declined and he was unable to tolerate cabozantinib; a dose reduction was attempted but he could not continue the drug due to continuous decline in intake and general health. He succumbed to progressive disease and cachexia within 3.5 months of palliative RT, and approximately 4 years from the first diagnosis of metastatic disease.

Case 2

A 56 year-old-patient, diagnosed radiologically to have ADPKD while being evaluated for hypertension 3 years previously, presented with oliguria for 3 months and azotemia (serum creatinine 11.87 mg/dL) with a diagnosis of CKD stage V on maintenance hemodialysis two to three times per week. Ultrasound and CT abdomen suggested bilateral renal exophytic, solid-cystic lesions, suggestive of RCC (►**Supplementary Fig. S1**). In view of preexisting poor renal function, bilateral laparoscopic radical nephrectomy was performed. On histopathology, left upper pole renal mass was suggestive of papillary RCC, type1 (pT1N0) with ADPKD. Right renal mass showed oncocytoma with ADPKD. Six months postoperatively, he developed extensive skeletal and abdominal nodal metastases. He was determined to have intermediate risk disease. Systemic therapy with pazopanib was initiated but within 6 months, there was progression of bony lesions and development of new pulmonary nodules and pleural effusion. He received palliative RT to painful pelvic bone metastases (8 Gy in single fraction) and switched to second-line therapy with lenvatinib/everolimus combination. However, there was rapid deterioration in his general health, and he succumbed to his illness within 3 months of initiating second-line systemic therapy.

Discussion

The first description of RCC and ADPKD together was given in 1934 by Walter and Braasch.[8] Since then, over 60 cases of this association have been published in English literature.

The diagnosis of RCC in a background of ADPKD poses several challenges. An evolving focus of RCC in a background of multiple renal cysts and distorted architecture may be difficult to discern in early stages even on regular follow-up. Many patients have end-stage renal disease and may not have any additional symptoms related to malignancy before progression to advanced disease or development of metastases. Symptoms from malignancy such as pain, hematuria, mass effect, or hypertension may be confused with cyst rupture or hemorrhage.

A literature review of 25 cases of RCC in background of ADPKD compared to RCC in general population reported no gender predilection, earlier age at presentation (45 vs. 61 years), higher occurrence of fever as a presenting symptom (32% vs. 7%), with higher incidence of bilaterality, multicentricity, and sarcomatoid features.[9]

Surgical series in ADPKD have also documented multifocality and bilateral renal involvement with RCC. Papillary and clear cell RCC were the most common reported pathologic diagnoses in these series and nearly a third of patients had more than one histologic subtype.[5,6] Metastatic disease is noted in nearly 20 to 23% patients with RCC in the setting of ADPKD, possibly due to a delay in diagnosis.[9,10]

Distinguishing new RCC within ADPKD is particularly challenging. The only definitive suspicion could arise from

symptoms and findings related to metastatic disease. Ultrasound of kidneys may show complex cysts with or without internal debris or hemorrhage. ADPKD cysts have variable size and appearance on CT or MRI. Hemorrhage within these cysts can appear as higher density on CT or high intensity on MRI. However, none of these features are specific to development of malignancy. A serial change in appearance of a cystic lesion (more asymmetry, parenchymal change, or appearance of solid component) may indicate a malignant change. Contrast enhancement within the cyst wall that is thick and irregular, enlarged renal vein or inferior vena cava indicating possible venous tumor thrombus, para-aortic lymphadenopathy, or other lesions in liver or soft tissues may be soft pointers toward RCC. MRI may show high signal on T1-weighted images, low signal on T2, and diffusion restriction on diffusion-weighted imaging; these findings may also occur in cyst infections, and if fever is the presenting symptom, there may be more confusion than clarity.[10,11] When suspicion is high and both CT and MRI are indeterminate, open biopsy or nephrectomy may be necessary to exclude malignancy. Role of PET-contrast-enhanced CT (CECT) in diagnosis is also limited since kidneys physiologically excrete FDG as well and malignant cysts may not appear very different from ADPKD cysts and FDG uptake is only slightly higher than normal renal parenchymal uptake; however, it is definitely useful in metastatic disease.[12] Despite advances in imaging, most of the RCCs are noted not on imaging but incidentally at autopsy, nephrectomy before kidney transplant, or during excision of symptomatic cysts. Among our patients, case 1 was picked up due to metastatic disease; however, renal function was normal. Case 2 had end-stage renal disease and diagnosed with RCC within 3 years of CKD. The diagnosis of renal masses on CT in case 1 was challenging but PET-CECT helped in distinguishing malignant cysts from ADPKD cysts, while in case 2, the renal tumors were solid and exophytic on CT.

On biopsy, normal kidney, ADPKD cells, and RCC cells may be differentiated on morphology. ADPKD cysts may be seen as fluid-filled abnormal cavities or membrane-lined sacs with compression of adjacent parenchyma. The fluid arises from glomerular filtrate. In RCC, however, the cyst fluid may show neoplastic cells.[13] Both ADPKD and RCC may have overexpression of vascular endothelial growth factor (VEGF) and its receptors. Hypoxia is seen in both with consequent overexpression of hypoxia inducible factor-1-alpha signaling. In ADPKD as well as RCC, cyst and tumor cell growth and proliferation may be related to two important pathways: PI3K/AKT/mammalian target of rapamycin (mTOR) and Ras/Raf/ERK.

Additionally, majority of polycystic kidney tissue expresses the epithelial developmental antigen Exo1 while normal kidney and RCC do not.[14] RCC cells have highly increased expression of epidermal growth factor receptor and transforming growth factor-alpha; these are also expressed in ADPKD and normal kidney but to a much lesser degree.

The postulated hypotheses of RCC development in ADPKD include chronic renal injury favoring renal parenchymal genetic mutations with consequent malignant change, or hyperproliferation in ADPKD acting as a precursor to RCC.[15,16] None of these theories have been substantiated yet. Some studies also demonstrate increased apoptosis in cystic and noncystic structures in ADPKD, negating the malignant potential in this condition.[17]

Clinical series documenting the clinical course of RCC in ADPKD are sparse. A Japanese study of 10 patients with a mean age of 61.2 years (80% men) and on hemodialysis for a mean of 11.2 years showed that clear cell carcinoma was the most common histologic subtype.[15] Three patients had bilateral disease, and four had multiple metastases. At a median follow-up of 20 months, 60% had died.

TCRC is a recently established rare histologic type recognized by the American Joint Committee on Cancer in 2010 and formally included as an independent subtype of RCC classification by The World Health Organization in 2016.[18,19] These tumors were earlier clubbed with collecting duct carcinomas, but now deemed a distinct entity, with a male predilection, indolent behavior, and diagnosis at early stage. Immunohistochemistry with vimentin, p53, and alpha methyacyl CoA racemase overexpression and negative high molecular weight cytokeratin, distinguishes them from other RCCs.[20] Metastases are rare and reported in less than 5 cases of the total 80 cases reported so far. Case 1 in this report is the first instance of an association between the rare TCRC and ADPKD. Indolent behavior is evident in this case—although TCRC was not identified initially in biopsy at 10 years and noted in biopsy review later, metastases took nearly 16 years to develop without any anticancer therapy. Surgery is the recommended therapy for TCRC. Targeted therapy has no documented role but a few case reports suggest partial response to sunitinib and everolimus.[21] The role of RT in RCC is largely palliative (for control of brain metastases or painful bone metastases) except in situations where oligometastatic disease is present and may be addressed with stereotactic body radiation therapy with or without immunotherapy.[22]

The surgical and pathology details of the second case have been discussed in a prior publication.[23] Association with papillary RCC has been hypothesized due to pathologic similarity of papillary epithelial cells to cyst lining hyperplastic cells that often manifest papillary-like change.[24] Although papillary RCC is believed to have a better prognosis than clear cell RCC, our patient (case 2) developed metastases fairly early (within 6 months of diagnosis).

Treatment for localized RCC in ADPKD would essentially include surgical management—partial nephrectomy in those with normal renal function and radical nephrectomy, often bilateral, for those with end-stage renal disease on dialysis. Some authors suggest that detection of RCC in one kidney in ADPKD should prompt aggressive search for tumor in the opposite kidney as well.[25] Patients who are not candidates for surgery may be considered for other local ablative therapies such as radiofrequency ablation to the gross tumor.[26] Follow-up for recurrence is again as big a challenge as initial diagnosis but periodic imaging (abdominal CT) is recommended. The European Society of Medical Oncology

guidelines recommend annual CT scan of chest and abdomen in low-risk patients and CT every 3 to 6 months for initial 2 years in high-risk patients. Metastatic RCC patients on systemic therapy should undergo CT imaging every 2 to 4 months.[27] Systemic therapy for patients with metastatic disease is guided by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification, comorbidities, and financial arrangements of insurance or reimbursement (especially if immunotherapy is being considered).

mTOR pathway undergoes activation after acute renal injury (or diabetes, progressive renal disease, etc.) and is responsible for repair and regeneration of injured renal tissue.[28] mTOR is inappropriately active in renal epithelial cells lining the cyst walls in ADPKD and mediates formation and enlargement of cysts. In normal kidneys, mTOR pathway inhibitors delay renal function recovery after acute insult, leading to chronic renal disease. In ADPKD, however, mTOR inhibitors have shown reduction in cyst volume and slowing of renal function decline.[29] mTOR inhibitors are also shown to be effective either alone or in combination with VEGF-targeted agents in metastatic RCC. Theoretically, this should be the preferred therapy especially in nonclear cell poor risk RCCs in background of ADPKD because of their dual activity.[30]

Both our patients received VEGF-targeted therapy as first line—case 1 due to financial challenges with immunotherapy chose oral tyrosine kinase inhibitor even for second and third line; moreover, the diagnosis of TCRC does not have a clearly defined systemic therapy. Our first patient did reasonably well on two lines of multikinase inhibitor therapy but progressed rapidly on third line, while the second patient had a rapid decline following initiation of second-line therapy that included mTOR inhibitor.

Conclusion

RCC in background of ADPKD is a difficult diagnosis and needs a high index of suspicion for clinical symptoms and signs, as well as imaging findings on screening of patients with known ADPKD. The association seems sporadic at present although several genetic mutations and pathways are being explored. RCCs in ADPKD kidneys are more often bilateral, multicentric, and metastatic compared to those in general population. Although various histologic types are described, the association of ADPKD with TCRC has been described for the first time in this report. Management of ADPKD essentially includes surveillance for renal function, and dialysis if CKD develops. RCC local management is guided by stage at diagnosis and baseline renal function, and systemic therapy by IMDC risk group as well as logistics. For those with localized disease and preserved renal function, partial nephrectomy is considered with surveillance imaging for recurrence.

Ethics Approval and Consent to Participate

Written informed consent was taken from patients at the time of treatment planning for future use as long as name was not disclosed. All ethical principles according to Helsinki guidelines were followed.

Consent for Publication

Yes, written consent to participate and publish this information was taken from the patients during the treatment.

Availability of Data and Material

Data can be made available by authors on reasonable request.

Authors' Contributions

P.V. wrote the paper and collected the data. S.G. designed the work, planned the treatment of patient and follow-up, revised and approved the final manuscript. R.M. participated in clinical decision-making, helped in writing and revision of the paper. N.K. and R.S. did the histopathological examination, made the diagnosis, and helped with pathology details for the paper. K.P. and R.K. participated in clinical decisions, and reviewed the final manuscript. All the authors read and approved the final manuscript.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgments

None declared.

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Tamoxifen-Induced Cutaneous Vasculitis—A Rare Case Report with Review of Literature

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Ind J Med Paediatr Oncol 2024;45:194–197.

Abstract

Tamoxifen is a selective estrogen receptor modulator and forms the mainstay of endocrine therapy in premenopausal women with breast cancer in both adjuvant and metastatic setting. Common adverse effects are menopausal symptoms with venous thrombosis and endometrial carcinoma being rarer but more sinister complications. Vasculitis is a rarely reported reaction to tamoxifen. We report a case of a 38-year-old woman with locally advanced breast cancer, who received neoadjuvant chemotherapy followed by modified radical mastectomy and adjuvant paclitaxel. She was on maintenance tamoxifen and leuprolide for 3 months, when she presented with pruritic bilateral maculopapular rash over all her limbs, legs more than hands. A skin biopsy from the left lower limb confirmed the diagnosis of vasculitis. Tamoxifen was stopped, and patient was switched to letrozole and leuprolide. She was given antihistamines, antibiotics, fusidic acid, vitamin C, and topical steroids. The lesions resolved completely in 1 month after stoppage of tamoxifen. We report this rare side effect of tamoxifen so that oncologists can effectively diagnose and treat this distressing but reversible condition.

Keywords

- tamoxifen-induced vasculitis
- breast cancer
- endocrine therapy
- side effects of tamoxifen

Introduction

Tamoxifen is a selective estrogen receptor modulator and has agonistic as well as antagonistic actions on the estrogen receptors (ERs), depending on the organ site. It binds to the ER of the tumor, preventing the binding of estrogen and hence interrupting the tumor proliferation pathways, leading to cell death.[1] It is the backbone of hormonal therapy in premenopausal women in the adjuvant as well as metastatic settings and is one of the landmark discoveries in the treatment of hormone receptor positive breast cancer, providing a significant benefit in disease free and overall survival.[2–4]

It is usually well tolerated. In addition to antitumor responses, tamoxifen can also exert antiangiogenic effects.[5] The common side effects seen are vasomotor symptoms (hot flushes), vaginal dryness, and menstrual irregularities with venous thrombosis, and endometrial carcinoma being less common. Cutaneous side effects account for 19% of the patients being treated with tamoxifen, including the vasomotor symptoms, and other less common effects like urticaria, rarely hypersensitivity-type reactions, including angioedema.[4] These are well documented and hence easily recognized by clinicians over the world. However, skin rash in current literature is documented less than 1%,[2] and cutaneous vasculitis is a rare and lesser-known reaction, hence may be overlooked and under treated.

As in most drug-induced vasculitis, there are antibodies produced against the drug molecule, which result in immune complex formation. Cutaneous vasculitis is a small-vessel hypersensitivity vasculitis, due to the deposition of these immune complexes in the vessel walls and activation of the inflammatory pathways. Typically, it presents as symmetric palpable purpura and affects dependent areas of the body.

article published online
May 8, 2023

DOI https://doi.org/10.1055/s-0043-1768181.
ISSN 0971-5851.

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

The clinical manifestation ranges from a mild cutaneous rash to a severe fatal reaction. It is important to recognize the offending agent, as usually discontinuation of tamoxifen leads to a rapid resolution of symptoms.[6] We report a case of a 38-year-old woman presenting with cutaneous vasculitis while on maintenance tamoxifen in the adjuvant setting.

Case Report

A 38-year-old premenopausal lady, with no family history and no comorbidities, presented with locally advanced carcinoma of the left breast, stage cT4bN2aM0. It was an infiltrating ductal carcinoma grade 3, which was hormone receptor positive (ER, progesterone receptor Allred score 8/8) and HER2neu negative. She received neoadjuvant chemotherapy with four cycles of adriamycin and cyclophosphamide, following which she had a modified radical mastectomy. The pathological stage was ypT2 ypN3a. She then received four cycles of paclitaxel, followed by radiation to chest wall and supraclavicular fossa along with which she was started on tamoxifen 20 mg once daily (OD) and leuprolide 11.25 mg once in3 months. Three months later she presented with maculopapular rashes on all four limbs, on her legs more than her hands (►**Fig. 1**). This rash was non blanching, erythematous, pruritic, and was not associated with any other systemic or infectious symptoms. Patient had no history of insect bite, or previous allergic reaction or family history of the same. Other causes of cutaneous vasculitis such as antineutrophilic cytoplasmic antibody (ANCA)-associated or autoimmune vasculitis were differential diagnosis; however, patient could not get the perinuclear-ANCA serum test done due to financial constraints. Using the Naranjo scale for causality assessment, this patient scored 6, which indicated a probable adverse drug reaction to tamoxifen.[7] This rash was Common Terminology Criteria for Adverse Events grade 1.

A dermatology opinion was taken, and skin biopsy was done from the left leg, in which perivascular mononuclear inflammation in superficial and deep dermis was found, with red blood cell extravasation and neutrophilic infiltration in the vessel walls. A diagnosis of small vessel vasculitis secondary to tamoxifen was then done (►**Fig. 2**). Tamoxifen was stopped, and she was given letrozole 2.5 mg OD along with the ovarian suppression. She was given antihistamines (cetirizine) and fusidic acid for a week, after which she was prescribed halobetasol 0.05% for topical application, along with vitamin C and moisturizing lotions, for a period of 2weeks. The symptoms resolved completely within 1 month and the patient was continued on letrozole with leuprolide.

Discussion

Drug-induced vasculitis is a reaction known to occur with many drugs documented in literature. The manifestation may vary, commonly from mild cutaneous vasculitis to rarely, severe systemic vasculitis with organ failure (Stevens-Johnson syndrome). Withdrawal of the drug often leads to resolution, which suggests a reversible pathogenesis. Vasculitis causes inflammation, fibrosis, weakening, and narrowing of the blood vessels. It is often difficult to distinguish between idiopathic and drug-induced vasculitis, but the temporal association with drug intake along with its resolution on withdrawal helps cinch the diagnosis and hence prevent further episodes. It has been noted that a timely withdrawal of the drug leads to complete relief of symptoms, but a delay in diagnosis may lead to persistent symptoms with the need for immunosuppressive agents.[8]

Drug-induced vasculitis may be small vessel, medium vessel, large vessel, or cerebral. Small vessel vasculitis is the most common type, and may be further classified into three types, namely cutaneous leukocytoclastic vasculitis (CLCV), immunoglobulin A (IgA), and ANCA-associated vasculitis. CLCV is the most frequently seen and is associated

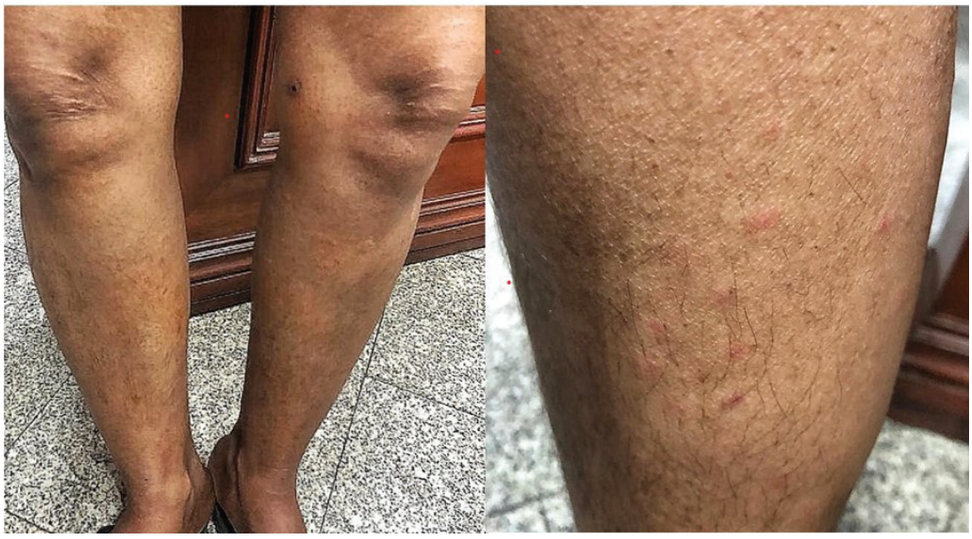

Fig. 1 Bilateral lower leg showing maculopapular rash.

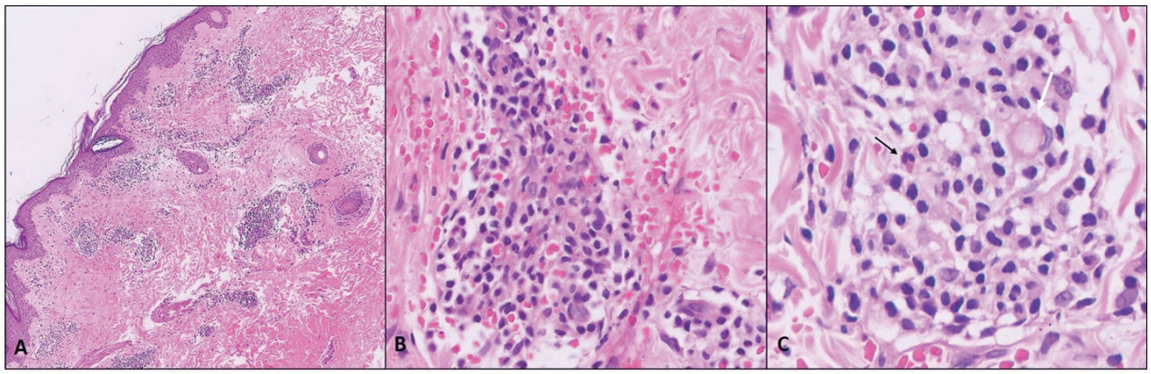

Fig. 2 Skin biopsy micorphotographs: (**A**) Dense perivascular inflammation around upper and mid-dermal vessels (hematoxylin and eosin [H&E] x100); (**B**) inflammatory infiltrate of lymphocytes, neutrophils, eosinophils, and plasma cells. Red blood cell extravasation with hemosiderin staining (golden brown). Vascular outlines not clear (H&E, x400); (**C**) vessel wall fibrinoid necrosis (white arrow) and eosinophil (black arrow).

with drug intake 31% of the time, mostly with antibiotics and anti-inflammatory drugs. CLCV may be associated with a significant number of patients having a synchronous involvement of internal organs, gastrointestinal tract, renal system, and musculoskeletal system.[9] In one study, nearly half of the patients required immunosuppressive therapy despite stopping the causative drug.[10] Other drugs known to cause CLCV are allopurinol, thiazides, phenytoin, sulfonamides, as well as drugs used in oncology like levamisole and ceritinib.[11] Other small vessel vasculitis (IgA and ANCA associated), as well as medium vessel vasculitis (often seen with tetracyclines, affecting renal and mesenteric vessels) and large vessel vasculitis (reported with bevacizumab and lenograstim, causing aortitis and periaortitis) are extremely rare forms and have only been reported anecdotally.

The pathogenesis of drug-induced cutaneous vasculitis involves immune complex formation and deposition in the cutaneous capillaries. This causes endothelial injury and the beginning of the inflammatory cascade, via activation of the complement system.[10] Due to the scarce available literature on the phenomenon, the exact pathogenesis of tamoxifen-induced vasculitis is not known. ANCA may also play an important role in drug-induced vasculitis, and many studies have established the association between ANCA positive vasculitis and prior drug use. The majority of ANCA-positive vasculitis related to drugs has been associated with perinuclear-ANCA pattern, in which myeloperoxidase is the most frequently related antigen.

Estrogen is agonistic in breast tissue and consequently in malignant breast cells and blood vessels. Tamoxifen blocks this action at the breast tissue level, and hence acts as an antagonist to estrogen. It is the mainstay of hormonal therapy in breast cancer in premenopausal women. It is given to all women with hormone receptor positive tumors due to its excellent tolerability and lower adverse effect profile. It has shown a benefit in adjuvant setting, metastatic setting, and also in preventing recurrence in the ipsilateral as well as contralateral breast. The benefit of extending tamoxifen therapy up to 10 years has been proven in multiple trials,[12,13] making its extended use more common, and subsequently its side effects with the knowledge of their management, more pertinent.

In our case, cessation of the offending agent along with symptomatic treatment using anti histamines and topical steroids led to a complete resolution of the symptoms within 3 to 4 weeks. Our patient did not require any further treatment or immunosuppressants, and was switched to letrozole along with ovarian suppression therapy, using gonadotropins. Joseph et al found a similar reaction and discontinued the use of tamoxifen too, after which the patient had a rapid resolution of symptoms.[6] Kulkarni et al observed a similar case and used dapsone in the treatment, while the tamoxifen was continued and vasculitis persisted.[14]

The strengths of this approach are that an early diagnosis exists of a rare but curable condition while preventing its complications, by quick and timely identification and intervention. The limitations include the fact that the use of tamoxifen is on a decline worldwide due to the introduction of newer agents, and the use of ovarian suppression with aromatase inhibitors is practiced commonly, for its survival benefit over tamoxifen.

Conclusion

Tamoxifen-induced cutaneous vasculitis is a rare complication manifesting as a simple drug-induced rash. While hot flushes, pruritus, mild rashes, and vaginal dryness are known common side effects of tamoxifen, it is important to distinguish them from cutaneous vasculitis. Prompt diagnosis of this infrequent condition may lead to a timely intervention and avoid immunosuppressants with their associated morbidity and complications in our patients. The intervention is simple, involves cessation of tamoxifen and its replacement with other endocrine therapies. It is, therefore, essential that all oncologists be aware of this ailment and its management.

Authors' Contributions

S.J. contributed to conceptualization, designing, definition of intellectual content, manuscript editing, and manuscript

review. A.D. helped in literature search, clinical studies, data acquisition, and manuscript preparation.

Patient Consent

Patients consent was taken for use her clinical images and data for publication.

Funding

None declared.

Conflict of Interest

None declared.

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