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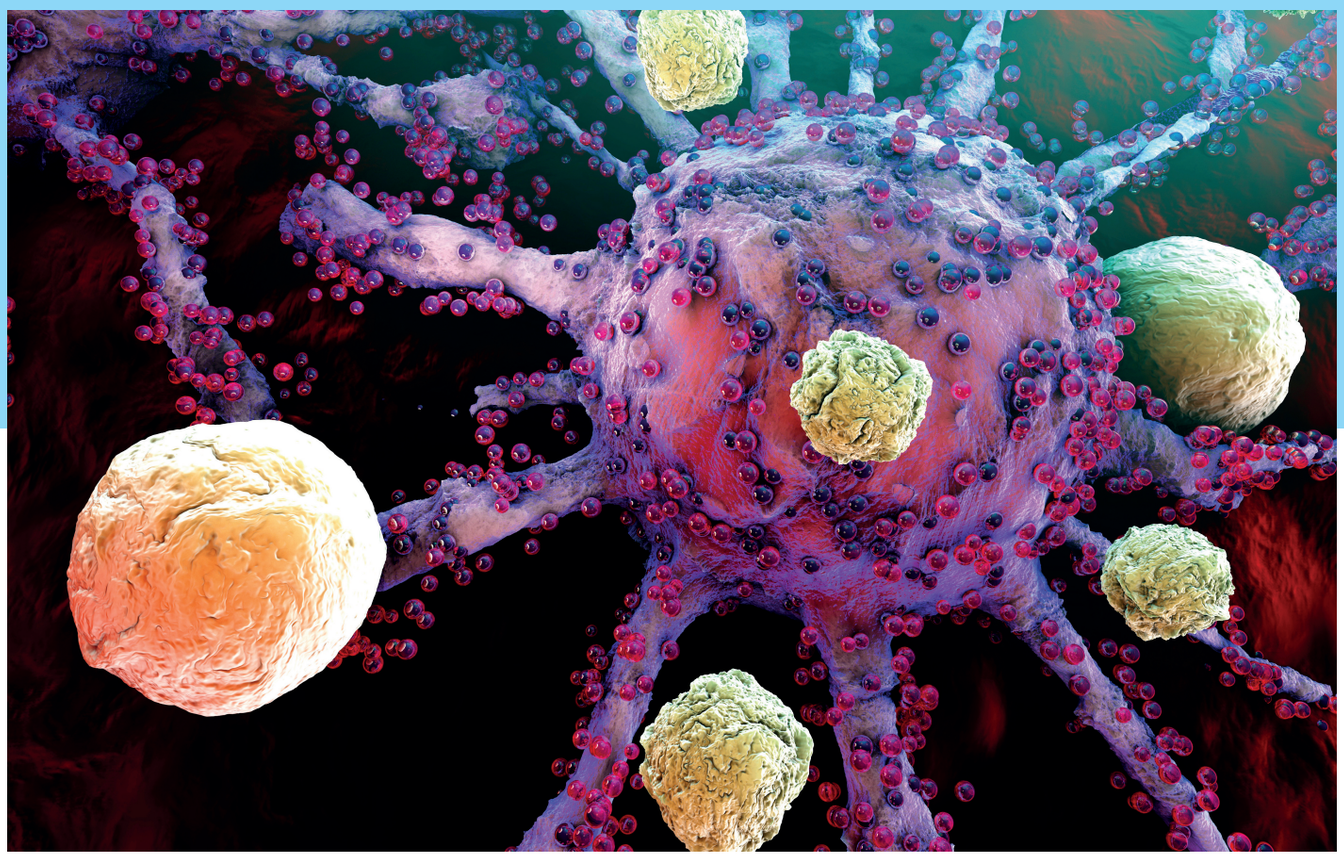

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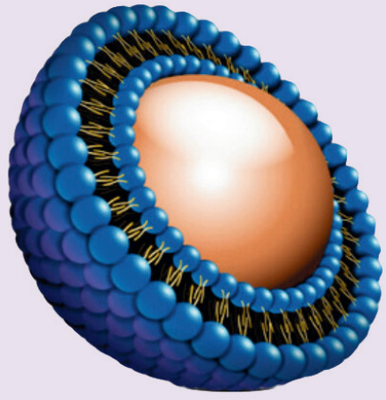

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The Role of Bosutinib in Chronic Myeloid Leukemia: An Indian Perspective

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Abstract

Management of chronic myeloid leukemia (CML) has been transformed by the use of tyrosine kinase inhibitors (TKIs). Presently in India, five TKIs are approved for the management of CML with distinct safety profiles. The selection of TKIs for chronic phase (CP)-CML patients is based on treatment goals, underlying comorbidities, and specific TKI toxicity profiles. Bosutinib is one of five TKIs indicated for the first-line treatment of CP-CML and patients with intolerance or resistance to prior TKI therapy. It possesses a distinct safety profile among other TKIs, with less cardiovascular adverse events (AEs), albeit the liver-related and gastrointestinal AEs have higher occurrence. The safety and efficacy of bosutinib have been examined in clinical trials; however, there is a paucity of data from Asia. A virtual expert panel meeting was convened to gather expert opinion from India on the selection of bosutinib as a treatment choice for patients with CP-CML. This is a white paper document drafted with the help of an expert panel of 14 oncologists and hematooncologists from India on bosutinib use in CP-CML. The experts concurred that bosutinib has proven efficacy for CP-CML in global randomized clinical trials and is well suited for CP-CML patients with existing cardiovascular comorbidities. However, it was not recommended for patients with gastrointestinal, pancreatic, or renal abnormalities. This review aims to put forth expert opinion and guidance document on key considerations for CP-CML clinical decision-making in India.

Keywords
- chronic myeloid leukemia
- India
- bosutinib
- tyrosine kinase inhibitors
- chronic phase

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Introduction

Chronic myeloid leukemia (CML), a myeloproliferative neoplasm, is characterized by an abnormal increase in circulating granulocytes as well as bone marrow myeloid precursors.[1,2] It is associated with Philadelphia chromosome (Ph+), a reciprocal translocation between a chromosome 9 gene–Abelson murine leukemia (ABL) and a chromosome 22 gene–breakpoint cluster region (BCR) (t[9;22][q34;q11]), forming the BCR–ABL fusion gene.[1,2] The disease presents itself in three stages—chronic phase (CP)-CML, accelerated phase (AP)-CML, and blast phase (BP)-CML. Majority of the patients are diagnosed during the CP-CML phase; however, untreated patients advance to the aggressive forms, AP-CML or BP-CML.[2–4] According to the American Cancer Society, CML constitutes 15% of the total leukemia cases.[3,5] According to a 2009 review, in India, the annual frequency of CML was estimated to be 0.8 to 2.2 per 100,000 population,[6] while a 2011 regional registry study results presented an age-adjusted rate (per 100,000) of 0.53 in females and 0.71 in males.[7] According to the 2018 Globocan survey, the incidence of leukemia in India was estimated to be 42,055 cases and the 5-year prevalence across all ages was 105,592 cases.[8]

The management of CML has been revolutionized by the use of tyrosine kinase inhibitors (TKIs) leading to the reduction in all-cause mortality rate and better long-term outcomes for patients with CML.[9] The TKIs approved for the management of CP-CML have varied safety profiles. The first-generation TKI-imatinib, second-generation TKIs-nilotinib, bosutinib, and dasatinib, and third-generation TKI ponatinib are the approved TKIs in India.[10,11] Bosutinib and ponatinib are the newest additions to the treatment armamentarium of CML.[12,13] The National Comprehensive Cancer Network (NCCN) guidelines recommend determining the risk status of patients with CP-CML using any relevant scoring system before initiating TKI therapy (►**Table 1**).[2] The choice of first-line therapy (bosutinib, imatinib, dasatinib, or nilotinib) for CP-CML is tailored according to the patient's risk profile and existing comorbidities. The ultimate treatment goal of TKI therapy is to achieve major molecular response (MMR) and possibly deep molecular response (DMR). The MMR is equivalent to a 3-log reduction ($\leq$0.1% BCR–ABL1 international scale [IS]) from the 100% baseline for untreated patients that includes molecular response [MR] 3, defined as $\geq$ a 3-log reduction in BCR–ABL1 transcripts from baseline.[14] While DMR is defined as BCR–ABL1 $<$0.01% IS[2] that includes MR 4/MR 4.5 defined as $\geq$ 4 or 4.5log reduction in BCR–ABL1 transcripts from baseline. Recent European LeukemiaNet recommendations 2020 highlight treatment-free remission (TFR) as a vital goal in CML. TFR can be achieved in CP-CML patients with a suitable response to first-line TKI with a duration of $>$5 years) and a DMR duration of over 2 years.[3]

Bosutinib Overview

Bosutinib presents BCR–ABL1 kinase inhibitor activity against BCR–ABL1 mutants, except V299L and T315I.[15] Bosutinib inhibits both Src and ABL tyrosine kinases.[16] Bosutinib can ablate BCR–ABL phosphorylation at low concentrations as compared with imatinib.[16] Food and Drug Administration (FDA) approved Bosutinib in 2012 for the treatment of adult patients with chronic, accelerated, or blast phase CML with intolerance or resistance to prior therapy. In 2017, the FDA approved bosutinib for newly diagnosed CP-CML patients.[12] Bosutinib is approved to treat patients with newly diagnosed CP-CML at a dose of 400 mg once daily (QD) and for CP, AP, or BP-CML patients with resistance/intolerance to prior therapy at a dose of 500 mg orally QD.[12]

Methods

A virtual expert panel meeting was convened involving 14 hematooncologists and medical oncologists from across India. All experts possess extensive hematooncology expertise in treating CML patients with approved TKIs. The expert opinion was derived from a moderator-initiated discussion with the panel of experts on bosutinib use in the treatment of CML. The experts discussed diverse topics on bosutinib such as treatment management, risk management, switch from other TKIs in first-line and second-line therapy, use in elderly and vulnerable population, use in patients with comorbidities, and TFR. The opinions gathered from the expert discussions are presented in this publication.

Treatment Decisions for Newly Diagnosed Chronic Myeloid Leukemia

The first-line TKI's approved for patients with CP-CML across all risk categories is Imatinib (400 mg daily), while the second-generation TKIs include dasatinib, 100 mg QD; nilotinib, 300 mg twice daily; and bosutinib, 400 mg daily.[17–19]

The experts discussed treatment initiation with second-generation TKIs, in patients with very recently diagnosed CP-CML in any of the risk groups (low risk, intermediate risk, or high-risk), AP-CML and BP-CML, and the choice of bosutinib in freshly diagnosed CP-CML patients.

With the accessibility to more potent TKIs, second-generation TKIs are preferably chosen for intermediate and high-risk CP-CML patients. The majority of the experts agreed that bosutinib could be the preferred TKI for intermediate and high-risk CP-CML. In BFORE trial, the MMR rate was higher with bosutinib than imatinib at 12 months (47.2 vs. 36.9%, respectively; $p = 0.02$), as was the cytogenetic response (CCyR rate) at 12 months (77.2 vs. 66.4%, respectively; $p = 0.0075$). Cumulative incidence was favorable with bosutinib (MMR: hazard ratio [HR], 1.34; $p = 0.0173$; CCyR: HR, 1.38; $p = 0.001$), with faster response times. Fewer patients experienced disease progression to BP-CML or AP-CML with bosutinib compared with imatinib (1.6 and 2.5%, respectively; ►**Table 2**).[19] Also, for patients with cardiovascular comorbidities (such as arrythmias, high blood cholesterol, coronary artery disease, and thrombosis), vascular abnormalities (such as pulmonary hypertension), and diabetes mellitus, bosutinib could be the preferred choice of TKI owing to its safety profile.[20,21] The panel of experts opined that for recently diagnosed CP-CML patients with existing

Table 1 Scoring systems and risk definitions

Scoring systems	Calculation	Low risk	Intermediate risk	High risk
SOKAL score	Exp $0.0116 \times (\text{age} - 43.4) + 0.0345 \times (\text{spleen size} - 7.51) + 0.188 \times [(\text{platelet count}/700)^2 - 0.563] + 0.0887 \times (\text{blood blasts} - 2.10)$	<0.8	0.8–1.2	>1.2
ELTS score	$0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen size} + 0.1052 \times \text{peripheral blood blasts} + 0.4104 \times (\text{platelet count}/1000)^{0.5}$	<1.5680	1.5680–2.2185	>2.2185
EUTOS score	$4 \times \text{Spleen size} + 7 \times \text{basophil count}$	≤87	NA	>87

Abbreviations: ELTS, European treatment and outcome study for CML long-term survival; EUTOS, European treatment and outcome study; Exp, exponential function.

Table 2 Comparison of treatment outcomes with first-line and second-line TKI therapy

Trial/Source	Tyrosine kinase inhibitors	Median follow-up (years)	Number (*n*)	Disease progression	Treatment outcomes			
					CCyR	MMR	PFS	OS
IRIS[50]	Imatinib 400 mg QD	11	553	7%	83%	–	92%	83%
DASISION[18]	Dasatinib 100 mg QD	5	259	5%	–	76%	85%	91%
	Imatinib 400 mg QD		260	7%	–	64%	86%	90%
ENESTnd[17]	Nilotinib 300 mg bid	5	282	4%	–	77%	92%	94%
	Nilotinib 400 mg bid		281	2%	–	77%	96%	96%
	Imatinib 400 mg QD		283	7%	–	60%	91%	92%
BFORE trial[19]	Bosutinib 400 mg QD	1	268	2%	77%	47%	–	–
	Imatinib 400 mg QD		268	3%	66%	37%	–	–
Shah et al[51]	Dasatinib 100 mg QD	7	Imatinib-R ($n = 124$)	–	–	43%	39%	63%
			Imatinib-I ($n = 43$)	–	–	55%	51%	70%
Giles et al[52]	Nilotinib 400 mg QD	4	Imatinib-R, $n = 226$; Imatinib-I, $n = 95$	–	45%	–	57%	78%
Cortes et al[53]	Bosutinib 400 mg QD	4	Imatinib and dasatinib-R ($n = 38$)	–	22%	–	–	67%
			Imatinib and dasatinib-I ($n = 50$)	–	40%	–	–	80%
			Imatinib and nilotinib-R ($n = 26$)	–	31%	–	–	87%

Abbreviations: CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukemia; I, intolerant; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; QD, once daily; R, resistance; TKI, tyrosine kinase inhibitor

renal toxicities (<30 mL/min/1.73 m^2), preexisting gastrointestinal disorders such as chronic gastritis, gastric ulcer, and inflammatory bowel disorders and with a history of pancreatitis, bosutinib may not be the preferred choice. Bosutinib has shown comparable efficacy with other second-generation TKIs,[22,23] and a better toxicity profile than dasatinib as exhibited in a recent study by Fachi et al.[24]

Switching to Bosutinib from Another Tyrosine Kinase Inhibitors

Treatment failure can occur due to point mutations in BCR–ABL1 kinase domain in CP-CML patients. The mutations E255K/V, F359V/I/C, and Y253F/H are sensitive to dasatinib/bosutinib, whereas the mutation F317L/V/I/C is sensitive to nilotinib/bosutinib; however, the T315I mutation is insensitive to all first and second-generation TKIs except ponatinib.[2,25–28] As per the NCCN guidelines, BCR–ABL kinase domain mutation analysis, drug interactions, and treatment compliance are recommended before initiating second-line TKI therapy.[2]

The experts concurred that switching of TKIs primarily occurs due to the development of drug-resistance, drug-intolerance, or suboptimal response. In a retrospective non-interventional study conducted in the hospitals of United

Kingdom and the Netherlands, 57% patients switched to bosutinib due to intolerance and 26% switched to bosutinib due to resistance to previous TKIs.[29] In a multicenter study in CML patients, the complete MR and MMR rates were 3.8 versus 27% for patients with imatinib and 41.5% versus 69% for patients switching to second-generation TKI, respectively, demonstrating increased chances of achieving DMR in switching to a second-generation TKI in CML patients demonstrating late suboptimal response with imatinib.[30] Development of nonhematological toxicities can also lead the physician to switch TKI. In a retrospective database study on CP-CML patients to assess toxicities with nilotinib and dasatinib, 29% patients experience treatment discontinuation owing to AEs (23%), disease progression (1%), or suboptimal response (2%).[31] AEs of grade 3 or 4 were observed in 54% on dasatinib and 22% of patients on nilotinib.[31] The most prevalent AEs with nilotinib were hyperbilirubinemia (47%) and Q-wave to T-wave (QT) interval prolongation (15%), whereas with dasatinib was pleural effusion.[31] Recent real-world and meta-analysis studies have shown that the new generation TKIs, dasatinib, nilotinib, and ponatinib pose a greater risk of cardiovascular toxicities than imatinib.[32–34] The experts agreed that BCR–ABL1 mutational status, the higher grade AEs, 1-log increase in BCR–ABL transcript level, and loss of MMR are reviewed while switching TKI.

The outcomes from a 2-year follow-up of a phase-I/II open-label study on bosutinib as a second-line TKI reported that 85% of patients achieved/maintained complete hematological response, 35% achieved MMR, and 59% achieved/maintained major cytogenetic response (MCyR), including 48% with CCyR. Moreover, the overall survival (OS) and progression-free survival (PFS) rates were 91 and 81%, respectively, after 2 years of treatment.[35] In another mature analysis of the phase-I/II open-label trial, which assessed factors that may influence long-term outcomes, BCR–ABL1 mutations were identified as a significant predictor of decreased OS (HR of 3.35).[36] In a comparison study of dasatinib, nilotinib, and bosutinib in second-line CML, bosutinib showed significantly greater PFS than dasatinib and nilotinib. In comparison to dasatinib, bosutinib resulted in HR for PFS and OS of 0.63 (0.44–0.90, $p < 0.05$) and 0.82 (0.54–1.26, $p = 0.37$), respectively, and an odds ratio (OR) for MCyR of 0.78 (0.53–1.16). However, in comparison with nilotinib, bosutinib demonstrated a significant HR of 0.54 (0.38–0.76, $p < 0.01$) in favor of bosutinib for PFS and a nonsignificant HR of 0.72 (0.46–1.13, $p = 0.16$) for OS (►**Table 2**).[37] Even in the advanced stages of CML (i.e., AP-CML or BP-CML), bosutinib has reported stable long-term efficacy and safety in patients experiencing prior treatment failure, as evident in the phase-I/II trial.[38] This trial indicated that 57 and 28% attained or maintained an overall hematologic response among AP-CML and BP-CML patients, and 40 and 37% attained or maintained MCyR by 4 years. The most commonly reported AEs were GI—low-grade diarrhea (any grade, 74%; maximum grade 1/2, 69%), while serious AEs occurred in 59% patients, most common being pneumonia (10%) and pyrexia (7%).[38]

Considering the switch to bosutinib from another TKI in second-line CP-CML, the experts agreed that loss of MMR, 1-log reduction in BCR–ABL percentage, or evolving BCR–ABL kinase mutations are the primary factors in switching to bosutinib from another TKI in second-line therapy. The experts highlighted that comorbidities and risk of potential AEs in the patient were also considered while choosing bosutinib over other TKIs.

Management of Adverse Events in Patients on Bosutinib

Skin rashes were reported in approximately 30% of the patients administered with bosutinib. However, they were usually short-lasting and well manageable. A study by Ault et al suggests comprehensive skincare and the use of topical agents, immunomodulatory agents, or systemic antibiotics for severe cases.[39] Diarrhea was reported as the most common AE in the Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial (67.7% patients),[20] BFORE trial (70.1% patients),[19] and in a recent real-world study on bosutinib (55% patients).[29]

Myelosuppression was comparable between bosutinib and imatinib arm in the BFORE trial (45.5 vs. 43.4%)[19] and BELA trial, where the incidence of thrombocytopenia was experienced in a similar percentage of patients (28 vs. 28%) as was the incidence of anemia (25 vs. 23%), while the incidence of neutropenia was lower in the bosutinib versus the imatinib arm (13 vs. 30%).[20] In the BFORE trial, musculoskeletal AEs were observed in fewer patients in the bosutinib arm (29.5%) than patients in imatinib arm (58.5%).[19]

Cardiac AEs (including atrial fibrillation, QT prolongation, and additional arrhythmias) were also comparable between the bosutinib arm and imatinib arm in BFORE trial with 5.2 versus 5.3% patients, respectively, and in phase-III BELA trial as 8 versus 6%, respectively.[19,20] After analysis of 4-year data from BELA trial, it was revealed that there is no increased risk of cardiovascular events with long-term bosutinib versus imatinib treatment.[20]

The experts concurred that diarrhea occurred early during bosutinib treatment, with the majority of patients experiencing transient, mild-to-moderate diarrhea. However, it is self-limiting in most cases and ceases to be a concern with time. In phase-II clinical trial results of bosutinib, only 10% of patients on bosutinib experienced grade 3/4 diarrhea, while others had mild (grade 1/2) diarrhea.[40] The practical management of bosutinib also suggests withholding bosutinib if a patient experience grade 3/4 diarrhea, that is, $\geq$7 stools/day during baseline/pretreatment until recovery to grade $\leq$1. Bosutinib can be resumed at 400 mg QD dose as patients recover to grade $\leq$1 diarrhea.[41]

The experts agreed that fewer cardiovascular AEs with bosutinib in trials and clinical experience may outweigh the safety concerns associated with bosutinib. Furthermore, the treatment regimen and dosage of bosutinib can be adjusted to manage the side effects. In routine clinical practice, bosutinib was either withdrawn for 2 weeks or the dose reduced by 100 mg when a patient experienced a hematological AE. The practical management of bosutinib also suggests withdrawing bosutinib when hematological AEs occur and resuming it at the same dose if patients recover

within 2 weeks. However, if the recovery takes more than 2 weeks, bosutinib dose must be reduced by 100 mg.[41,42] A phase-I/II study assessing the safety of bosutinib in the management of CML patients also reported toxicities such as alanine transaminase (ALT) elevations and lipase increases. However, these toxicities were successfully managed by treatment interruptions and dose reductions.[40] In hepatic toxicity, bosutinib is not withdrawn until the aspartate aminotransferase (AST) or ALT level increases by four to five times, and discontinued if the AST/ALT level increases further.[41,42]

According to experts, the renal profile of patients with CP-CML must be considered during treatment initiation and bosutinib dose must be recommended accordingly. Furthermore, the creatinine clearance level of the CP-CML patient should be regularly monitored during treatment. For creatinine clearance of 30 to 50 mL/min, a starting dose of 400 mg/d bosutinib is recommended, whereas for creatinine clearance <30 mL/min, it is 300 mg/d.[41]

Bosutinib in Patients with Underlying Comorbidities

Data suggest that patients diagnosed with CP-CML have at least one comorbidity during diagnosis. In an observational study conducted in patients with CP-CML, 78.1% patients had a Charlson comorbidity index (CCI) of 2. In comparison, 15.9% patients had a CCI of 3.[43] Most common comorbidities associated with patients with CP-CML were diabetes mellitus, peptic ulcer disease, peripheral vascular disease, liver impairment, renal insufficiency, myocardial infarction, tumors other than CML, cerebrovascular disease, or chronic pulmonary disease.[43,44] Accounting underlying comorbidities among patients with CP-CML at diagnosis is pivotal in therapy selection.

The experts agreed that bosutinib could be recommended for CP-CML patients with cardiovascular comorbidities, underlying diabetes, and pulmonary hypertension. They have observed positive outcomes in such patients with bosutinib use in routine clinical practice.

Bosutinib in Elderly and Vulnerable Population

CML is usually diagnosed at a median age of 57 to 60 years[45]; consequently, substantial proportion of patients with CML have achieved elderly status or are likely to achieve it during treatment. Increased age affects the OS of patients with CML. Bosutinib has proven effectiveness and favorable safety profile in elderly patients. In a retrospective real-world study of bosutinib use in 91 elderly (>65 years) patients with CP-CML, all grade hematological and extrahematological toxicities were reported in 13.1 and 49.4% patients, respectively, after 18.1 months median period of treatment.[46] Among the 86 elderly patients evaluable for response, approximately 4.6% achieved hematological response and 82.5% achieved CCyR (MCyR: 4.7%, CCyR: 77.9%).[46] Furthermore, bosutinib may be better tolerated at lower doses (300 mg QD) in elderly patients. In a prospective phase-II study in 63 elderly CML patients after intolerance/failure of first-line TKIs, bosutinib was initiated at a dose of 200 mg QD, increased to 300 mg QD after 3 months, and further to 400 mg QD in patients with BCR–ABL transcript >1%. Overall, 60% of the cohort achieved MR3 by 12 months, while 38 and 19% achieved MR4 and MR4.5, respectively.[47]

For younger patients, especially women, bosutinib which is a second-generation TKI may be preferred over imatinib, particularly because the achievement of a deep and rapid MR may allow eventual discontinuation of TKI therapy for fertility purpose. With the currently available management options for CP-CML, effective contraception is encouraged with all TKIs due to the risk of fetal complications with drug exposure in women of reproductive age. Overall, the experts agreed that bosutinib can be recommended for elderly patients, women of reproductive age, and patients with comorbidities such as cardiovascular disease, pulmonary hypertension, or diabetes mellitus.

Treatment-Free Remission with Bosutinib

In recent years, the treatment goals in CML have evolved, a group of patients successfully treated with TKI may experience a period of TFR. For patients with CML achieving DMR on TKI therapy, TFR is a safe treatment goal. TKI discontinuation involving imatinib, dasatinib, and nilotinib has been examined in recent studies, though there are limited data exploring TKI discontinuation with bosutinib. A U.S. study that evaluated the molecular recurrence of CML and patient-reported outcomes after discontinuation of TKI for patients in TFR at 6 months observed a moderate improvement in fatigue, diarrhea, and minimal increase in pain interference, while some patients reported substantial improvements in fatigue and diarrhea.[48] However, failing to achieve MR 4.5 before TKI discontinuation proved as a strong predictor of relapse with HR 40.23 in a single center study involving 15 patients with ponatinib/bosutinib discontinuation.[49]

The experts discussed their clinical experience with dasatinib and nilotinib and their opinion on the discontinuation of bosutinib once DMR is sustained for a certain period. The experts acknowledged that there is limited published literature on TFR with bosutinib and a pressing need for further research in this area. However, experts opined that based on NCCN guidelines, the data on TFR for other second-generation TKIs could be extrapolated for bosutinib.[2]

Conclusion

The article accentuates the unmet needs in CP-CML management in the country. The clinical opinions gathered from the participating experts may guide Indian oncologists in their day-to-day clinical decision-making for CP-CML. Bosutinib has a better safety and tolerability profile than other second-generation TKIs. Most AEs with bosutinib are low grade and controllable over time. Bosutinib has proven efficacy over imatinib in clinical trials and is an efficacious alternative for CP-CML patients in India. It emerged as a favored treatment of choice among the experts for CP-CML patients with underlying comorbidities and those at the risk of developing serious cardiac and pulmonary AEs.

Authors' Contributions

All authors adhered to the ICMJE authorship criteria. All authors reviewed and revised the manuscript for important intellectual content.

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Conflict of Interest

M.J.J. received grants from Viatris (Mylan) during the conduct of the study; he has also received grants from Novo Nordisk, Pfizer, Takeda, Grifols, Dr Reddy's Laboratory, Janssen and Janssen, and Mylan outside the submitted work. A.T.S. was an employee of Viatris (Mylan India) during the conduct of the study. N.R. is currently an employee of Viatris (Mylan India). A.T.S. was an employee of Viatris during the conduct of the study. M.J.J. reports grants from Viatris (Mylan), during the conduct of the study and others from Novonordisk, Pfizer, Takeda, Grifols, Dr Reddy's Laboratory, Janssen and Janssen, and Mylan, outside the submitted work. N.R. is an employee of Viatris that funded the study.

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Clostridium difficile in Oncology Patients—Review of Diagnosis and Management in the Indian Setting

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Abstract

Clostridoides (formerly *Clostridium*) *difficile* (*C. difficile*) is a toxin-producing, gram-positive anaerobic bacillus, commonly implicated in antibiotic-associated diarrhea and pseudomembranous colitis. The true burden of *C. difficile* infection is unclear in India, as it is likely underdiagnosed and underreported. Its incidence is much higher in oncology patients where it can contribute significantly to morbidity and mortality. There are several challenges in the Indian setting, including lack of uniform availability of testing infrastructure, as well as therapy. Oncology patients further present with a unique set of challenges. This article will review the approach to diagnosis and management of *C. difficile*-associated diarrhea in India, with a focus on oncology patients.

Keywords
- *Clostridium difficile*
- gram-positive anaerobic bacillus

Introduction

Clostridium difficile is a toxin-producing gram-positive anaerobic bacillus, commonly implicated in antibiotic-associated diarrhea (CDAD) and pseudomembranous colitis. CDAD remains a formidable problem in healthcare facilities across the globe. In 2011, close to half a million cases of *C. difficile* infection (CDI) were reported in the United States, with the majority of cases occurring in the elderly patients (over 65 years of age).[1] There is also a financial price to pay for these infections. A meta-analysis of 42 studies published in 2016 showed that CDI placed a significant financial burden on the US healthcare system.[2] In this study, the average and incremental length of stay for CDI in-patient treatment were 11.1 (90% confidence interval [CI]: 8.7–13.6) and 9.7 (90% CI: 9.6–9.8) days respectively. Total annual CDI-attributable cost in the United States was calculated to be US$ 6.3 (range: $1.9–$7.0) billion).[2]

CDI is a common problem in oncology patients. A retrospective review found that 17.3% of the 225 patients with solid tumors admitted to a hospital with diarrhea had CDAD.[3]

A multicenter survey of oncology units showed that the pooled rate of hospital-acquired CDAD in patients with cancer was more than twice the rate reported for all patients in the United States.[4]

The incidence of CDAD has been estimated to be between 7.1 and 30% in various Indian studies.[5–7] A study published in 2017 from India showed that out of the 791 patients with nosocomial diarrhea included, 6% had CDAD. Among these patients, malignancy was found to be the most common underlying condition.[8] A 2021 study from a tertiary care center in south India showed the prevalence of CDAD in cancer patients to be 18.67%.[9]

Due to the lack of large-scale data and multicentric studies, the true burden of this problem is unknown in India. Lack of uniform availability of testing infrastructure as well as access to therapy is among the challenges faced in Indian settings. Drugs such as fidaxomicin are not available, and modalities such as fecal microbiota transplantation (FMT) are not well established in most Indian hospitals. Oncology patients further present with their unique set of challenges.

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They have multiple risk factors for the development of CDAD; chemotherapy itself can lead to dysbiosis of the gut flora. Antibiotic exposure in these patients is generally frequent and can be for longer durations. These patients also have multiple hospital encounters leading to increase in incidences of nosocomial infections.

There are no national guidelines and there is lack of clarity regarding testing protocols for CDAD in India. Also, FMT is performed in very few centers in the country and there are no established protocols regarding donor screening and administration. This article reviews the approach to diagnosis and management of CDAD in India and sheds light on how we can overcome some diagnostic and therapeutic challenges, with a focus on oncology patients. It also suggests a protocol for performing FMT, and suggests various steps that can be taken by hospitals across the country to curb the problem of CDI.

Diagnosis of CDAD in the Oncology Population in India

Population Criteria for Testing

Diarrhea in the oncology patients can have a wide range of differential diagnoses. These can include:

- Chemotherapeutic agents
- Immunotherapeutic agents
- Surgery
- Radiation therapy
- Underlying malignancy
- Infectious causes, including *C. difficile*

Clinical Practice Guidelines for CDI issued by the Infectious Disease Society of America (IDSA) in 2017 recommend testing when the patient has had three or more unformed stools in the preceding 24 hours.[10] Other causes of diarrhea in this population need to be considered carefully before ordering a stool *C. difficile* assay.

Principles of Laboratory Testing

Pathogenicity of *C. difficile* to cause CDAD is associated with production of two toxins, that is, toxin A (enterotoxin) and toxin B (cytotoxin). Not all strains of *C. difficile* possess the gene locus containing *tcdA* and *tcdB* genes to express these toxins. Hence, the diagnosis of CDI is based on the detection of these toxins and not just the detection of bacteria.

Clinical utility of any modality of laboratory testing to "rule in" (positive predictive value—PPV) or "rule out" (negative predictive value) diagnosis of CDI depends on its specificity and sensitivity, respectively. It is also decided by the prevalence of the disease in a particular population, and hence, denotes the pretest probability of the disease. Since diarrhea in oncology patients can have numerous infectious and noninfectious differential diagnoses, exclusion of these before ordering a *C. difficile* test enhances the PPV of the test.

C. difficile colonizes the large bowel of the gastrointestinal (GI) tract. It can be a part of the normal gut flora of children less than 2 years of age, in whom colonization rates can exceed 40%.[11] Colonization rates as high as 30%[12] are also seen in adults with prolonged hospitalization, such as the patients hospitalized in the oncology units. This is another reason why exclusion of other etiologies is essential for the accurate clinical interpretation of positive results.

Modalities of Laboratory Testing

Variety of testing modalities are available for the diagnosis of CDI, as summarized in ►**Table 1**.

Approach to Laboratory Testing

Testing for stool samples should be limited to selection of "loose stool that takes the shape of the container." If other causes of diarrhea have not been ruled out, a multistep algorithm that uses glutamate dehydrogenase (GDH) antigen plus toxin assay arbitrated by NAAT or nucleic acid amplification test plus toxin assay rather than NAAT alone should be followed.

If other etiologies have been excluded, which increases the pretest probability of CDAD, then NAAT alone or the GDH plus toxin assay arbitrated by NAAT or NAAT plus toxin assay rather than toxin assay alone should be used. We propose the following algorithm based on IDSA guidelines that can be applied to oncology patients in India. (►**Table 2**)

►**Table 3** describes some other important diagnostic pearls, which are valuable in the Indian setting.

Diagnostic Challenges in Oncology Patients

Oncology patients have an increased risk of *C. difficile* colonization owing to increased healthcare exposures, use of antimicrobial, and chemotherapeutic agents. Hence, distinguishing between colonization and infection is critical in these patients. However, toxin assays may have a lower sensitivity in immunocompromised patients.[13] Hence, a polymerase chain reaction (PCR) test for detecting toxigenic strains may be required. The exact reason for this phenomenon is still being studied. In these patients, even a small amount of toxin (below the limit of detection of the assay) can cause clinically significant CDAD. Also, some of these patients may receive intravenous immunoglobulins as a part of therapy for their underlying disease, which may bind *C. difficile* toxins A/B.[13] A PCR test may not be available in many laboratories across the country, and when performed as a part of a GI syndromic PCR panel (multiplex panel), may escalate the cost of diagnosis.

Management of *C. difficile*-Associated Diarrhea in Oncology Patients in the Indian Setting

Therapy for the Initial Episode of CDAD

The 2021 IDSA guidelines on the management of *C. difficile* recommend fidaxomicin as the agent of choice for the first episode of CDAD.[14] Data suggests a higher cure rate and lower rates of recurrence for fidaxomicin compared with oral vancomycin.[15] However, the cost of therapy and lack of availability in India are prohibitive factors for the use of fidaxomicin. The guidelines state that vancomycin remains an acceptable alternative when oral fidaxomicin is unavailable.[14]

Table 1 Diagnostic modalities for *Clostridium difficile*-associated diarrhea (CDAD)

Testing modality	Basic principle	Sensitivity (SS)/ specificity (SP)	Advantages	Limitations
Toxigenic culture (TC)	Inoculation of stool on a selective/chromogenic medium	SS: 22–100% SP: 90% (6)	High sensitivity. Performance of drug susceptibility testing	Cumbersome to perform Need of technical expertise Prolonged turnaround time—around 1 week Low positive predictive value (PPV) due to growth of non-toxigenic strains
Cell culture cytotoxicity neutralization assay (CCNA)	Observation of cytopathic effect (CPE), cell rounding and neutralization of CPE with antitoxin	SS: 75–85% SP: 93–100% (7)	Reference gold standard for laboratory confirmation of *C. difficile* infection (CDI) Very high specificity	High level of expertise needed
Glutamate dehydrogenase (GDH) antigen	Detection of GDH enzyme secreted by *C. difficile* using: Rapid lateral flow immunochromatography Enzyme linked immunosorbent assay (ELISA) Enzyme linked fluorescence immunoassay (ELFA)	SS: 71–95% SP: 87–90% (8)	Easy to perform Rapid results Inexpensive Excellent sensitivity, can be used as a screening test	Positive results in both toxigenic as well as non-toxigenic strains, hence low PPV
Toxin A and B immunoassays (TIA)	Detection of toxin A and B in the specimen using: rapid lateral flow immuno-chromatography ELISA ELFA	SS: 60–86% SP: 91–98% (9)	Easy to perform Rapid results Inexpensive	Inconsistent sensitivity due to variations in strains and kits Cannot be used as the sole test for the diagnosis of CDI due to false negative results.
Nucleic acid amplification test (NAAT)	Exponential amplification and detection of tcdA and tcdB genes using real-time polymerase chain reaction (PCR) Cartridge based PCR assays LAMP (ligase mediated amplification) Multiplex PCR syndromic gastrointestinal panels	SS: 82–100% SP: 90–100% (10)	High sensitivity, specificity Rapid turnaround time Excellent negative predictive value (NPV)	Positive results may be obtained with colonization and needs clinical correlation

The recommended dose of oral vancomycin in nonsevere cases is 125 mg administered every 6 hours. A meta-analysis comparing less than 2 g of oral vancomycin per day versus more than 2 g of daily oral vancomycin did not find any significant differences in the rates of recurrence in the two groups.[16] Though rare, a handful of case reports have described detectable serum levels in patients administered oral vancomycin.[17] This is usually applicable to patients with an impaired renal function or those receiving high doses of oral vancomycin.

Fulminant or severe *C. difficile* is defined as CDAD with a total leukocyte count of more than 15000/mm^3, or with more than or equal to 50% increase in the serum creatinine. However, in the oncology setting, these parameters may be difficult to use as the patients may be neutropenic and may have other causes for renal impairment. Hence, the Zar score can be used (►**Table 4**), where a score of more than or equal to 2 indicates severe CDI.

Fidaxomicin has not been evaluated in fulminant (previously known as severe, complicated CDAD), and hence, the drug of choice in fulminant CDAD remains oral vancomycin (500 mg dose administered every 6 hours). For patients with ileus, 500 mg of vancomycin in 100 mL of normal saline can be administered as retention enema every 6 hours. Also, the addition of intravenous metronidazole can be considered.

Usually, the recommended duration of therapy for the initial episode is 10 to 14 days.

CDAD Refractory or Resistant to Vancomycin

Vancomycin resistance in the case of *C. difficile* has been described. A particular strain of *C. difficile* designated as BI/NAP1/027 is characterized by the presence of a binary toxin and deletions in the regulatory gene, *tcdC* and by resistance to moxifloxacin.[18] A report from Israel found that 87.7% of the ribotype 027 isolates had a vancomycin minimum inhibitory concentration more than 2 mg/L.[19] A

Table 2 Diagnosis of CDI in oncology patients

GDH antigen	Assay for toxin A	Assay for toxin B	Recommended approach and comments
Positive	Positive	Positive	Treat as CDAD
Positive	Positive	Negative	Treat as CDAD
Positive	Negative	Positive	Treat as CDAD
Negative	Negative	Negative	Do not treat as CDAD
Positive	Negative	Negative	May indicate colonization. If high clinical suspicion, PCR for *C. difficile* should be done in oncology patients; do not treat if PCR is negative.
NAAT			
Positive	Positive	Positive	Treat as CDAD
Negative	Negative	Negative	Do not treat as CDAD
Positive	Negative	Negative	Probable colonization if pretest probability low, do not treat as CDAD Probable CDAD if pretest high, treat as CDAD
Positive	Negative	Positive	Treat as CDAD
Positive	Positive	Negative	Treat as CDAD

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; CDI, *C. difficile* infection; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

Table 3 Other diagnostic pearls in the Indian setting

Do not perform repeat testing routinely within 7 days of the same episode of diarrhea, if initial test is negative
Repeat testing may be considered in patients with worsening of symptoms and a high index of clinical suspicion for CDI
Do not test for screening asymptomatic carriers
Episodes of recurrent CDI should be assessed by repeat testing
No value in testing to establish cure—more than 60% tests remain positive after successful therapy
Testing should not be routinely performed in the first 2 years of life unless clinical suspicion for CDAD is high

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; CDI, *C. difficile* infection.

Table 4 Zar score for fulminant (severe) CDAD

Factor	Points assigned
Age > 60 years	1
Body temperature > 38.3 C	1
Albumin < 2.5 g/dl	1
Endoscopic evidence of pseudomembranous colitis	2
Treatment in the ICU	2

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; ICU, intensive care unit.

pan European longitudinal survey from 2015 found that the epidemic ribotypes 027 and 001/072 were associated with multiple antimicrobial resistance of high levels.[20] Despite this in vitro observation, clinical response to vancomycin is noted in a majority of patients. This is likely due to the high colonic concentrations attained with proper dosages of oral vancomycin. However, this does point to a potential problem of emergence of clinically refractory cases in the future. It also highlights the need for adequate vancomycin dosing in these patients that ideally should be administered four times a day. The mechanism of resistance to vancomycin, however, remains unclear.[21] Amino acid changes in peptidoglycan biosynthesis-associated proteins such as MurG may play a potential role in the resistance to vancomycin.[22]

Therapy for *C. difficile* being refractory to vancomycin remains uncertain. Fidaxomicin as stated earlier is not freely available and its high cost is also prohibitive in the Indian setting. A prospective observational study by Popovic et al comparing the therapy of oral teicoplanin with that of oral vancomycin found that teicoplanin resulted in a significantly higher clinical cure rate compared with vancomycin.[23] Teicoplanin is freely available in India and can be a useful drug in the setting of vancomycin-refractory CDAD in India. A dose of 200 mg twice a day can be used in this setting. An ampule containing 200 mg/3 mL of teicoplanin can be directly given with 100 to 200 mL of water.

Other agents such as nitazoxanide, tigecycline, and rifaximin should only be used as salvage therapy, when other regimens have failed.

Management of Recurrent Episodes

Recurrence rates for CDAD can be as high as 25%. When available, fidaxomicin remains the drug of choice for a

recurrent episode. For the first recurrence of CDAD, vancomycin as a tapered and pulsed regimen should be used. A suggested regimen is oral vancomycin—125 mg, four times a day for 14 days; followed by 125 mg, twice a day for 1 week; then 125 mg daily for a week, later 125 mg every 2 to 3 days for 2 to 8 weeks. In a randomized control study, patients receiving rifaximin 400 mg three times daily for 20 days immediately after completing standard therapy for CDAD were found to have a lower recurrence versus those given placebo (15 vs. 31%).[24] For patients with multiple *C. difficile* recurrences, the therapeutic options include:

(i) Vancomycin as a tapered and pulsed regimen
(ii) Vancomycin (250 mg, every 6 hours for 10 days) followed by rifaximin (400 mg, every 8 hours for 20 days) and
(iii) FMT.

Should Other Antibiotics be Stopped in Oncology Patients with CDAD?

There is evidence to suggest that continuation of unorthodox antimicrobials to treat CDAD may lead to compromised initial response to CDI therapy and may reduce the durability of response.[25] However, in the case of cancer, this decision has to be taken after careful evaluation of the patient and ruling out other infections.

Monoclonal Antibody

The monoclonal antibody Bezlotoxumab (against the toxin B of *C. difficile*) is not available in India. It can be used in conjunction with antimicrobial agents that are active against *C. difficile,* especially in the elderly and immunocompromised patients.

Fecal Microbiota Transplantation (FMT) in the Indian Setting

The pathophysiology of CDAD involves intestinal dysbiosis. Hence, the use of FMT has garnered a surge in interest in the management of CDAD. Currently, FMT can be considered for the following indications:

- Recurrent CDAD
- CDAD which is refractory to antimicrobial therapy
- May be considered in severe or fulminant disease, though the data are limited

In a randomized trial of 232 patients with recurrent CDAD treated with FMT, the efficacy for one FMT was approximately 50% which increased to 75% for two FMTs performed and approximately 90% for more than two FMTs performed.[26]

FMT responses can be durable; in a retrospective study, almost 78% of the patients continued to show a good response at the end of 1 year.[27]

In the Indian setting, lack of stool banks and preformed capsules can pose a challenge. Stool inoculum from the donor needs to be freshly prepared before administration. Also, donor screening can be challenging, with high rates of bacterial colonization in the Indian population. This also needs to be balanced with cost constraints which may limit donor testing. ►**Table 5** outlines our institutional approach to selecting a donor for FMT. Scrupulous screening of the donor stool to exclude the presence of multidrug-resistant

Table 5 Suggested approach to donor selection for FMT in the Indian settings

Suggested clinical evaluation of the donor:
Should be off immunosuppressive therapy, chemotherapy, antimicrobial agents or proton pump inhibitors in the preceding 3 months
Should not have personal or family history of chronic gastrointestinal diseases
Should not have a history of HIV, syphilis, hepatitis B or C viral infections No personal history of cancer, including gastrointestinal cancers or polyposis syndrome, and first- degree family history of premature colon cancer
Previous tissue or organ transplant recipients are excluded
Suggested laboratory evaluation of the donor in the Indian setting:
Hemogram, liver function tests, CRP, ESR
HIV and VDRL
Hepatitis C antibody
Hepatitis A IgM antibody
Hepatitis B surface antigen
Routine stool examination for ova, cysts, and larvae
Stool bacterial culture and antibiotic susceptibility testing to exclude MDROs like ESBL and carbapenemase producing gram-negative bacilli, as well as vancomycin-resistant Enterococci
Modified ZN staining for cryptosporidium, isospora, and microsporidia
C. difficile assay

Abbreviations: CRP, C-reactive protein; ESBL, extended spectrum β lactamases; ESR, erythrocyte sedimentation rate; FMT, fecal microbiota transplantation; HIV, human immunodeficiency virus; IgM, immunoglobulin M; MDROs, multidrug-resistant organisms; VDRL, venereal disease research laboratory test (for syphilis); ZN, Ziehl–Neelsen.

Table 6 Suggested protocol of FMT solution preparation

At least 50 g of stool specimen is submitted by the donor on the day of FMT using sterile stool collection kit provided by the laboratory. Time of specimen voiding is noted
Donor stool sample is processed in biosafety cabinet, the technician donning aprons, impervious gown, and cap
Using sterile wooden spatula, 50 g of stools is emulsified in 250 mL of nonbuffered sterile saline (autoclaved in a screw capped glass bottle and cooled)
Emulsion is sieved through triple layered sterile gauze to filter out coarse particles (>1–2 mm). Resultant filtrate is collected in a sterile flask and transferred to the endoscopy suite with an airtight seal
FMT solution needs to be infused within 6 hours of donor voiding. The solution is stored at room temperature until the procedure
Patients should not be taking any antibiotics or probiotics 48 hours before FMT
If diarrhea persists 1 week after procedure, *C. difficile* NAAT testing should be done and repeat FMT may be considered if positive

Abbreviations: FMT, fecal microbiota transplantation; NAAT, nucleic acid amplification test.

microorganisms, parasites, and *C. difficile* is essential. ►**Table 6** gives a brief description of the protocol of FMT solution preparation followed at our center.[28]

Administration can be done via the upper or lower GI approach, though the American College of Gastroenterology 2021 guidelines favor the administration of FMT via a colonoscopy.[29] The safety of FMT in neutropenic patients has not been completely established and better-quality data are needed before this practice is adopted, especially in India. Here, donor stools may be frequently colonized with resistant pathogens increasing the risk of donor-derived infections.

Periprocedural cessation of antimicrobial agents (which is needed for FMT) can sometimes pose a challenge in immunocompromised patients.

Antimotility Agents

There is no definitive evidence to suggest that antimotility agents are contraindicated. In a retrospective study of 339 patients with hematological malignancies who had CDAD, it was found that the addition of antimotility agents to appropriate antimicrobial therapy does not pose any additional risk.[30]

Infection Control and Preventive Practices

Oncology units are especially prone to CDAD outbreaks. Asymptomatically colonized patients or healthcare workers can transmit the infection to the immunocompromised hosts.[31] Transmission can occur from a CDAD patient or an asymptomatic colonizer via the hands of the healthcare personnel. Spores of *C. difficile* can contaminate and survive on equipment, fomites, and the environment. Contaminated commode seats and bedpans are particularly associated with a high risk of transmission. Thorough and frequent disinfection of medical equipment and environmental surfaces with sporicidal agents like hydrogen peroxide or peracetic acid is an important preventive measure.[32] At our institution, we use peracetic acid for surface disinfection as well as in the event of an outbreak. Commonly used surface disinfectants like quaternary ammonium compounds or alcohol are ineffective in eradicating *C. difficile* spores.

Oncology patients who develop CDAD must be placed on contact isolation (private rooms with dedicated toilets). Barrier nursing precautions should be strictly followed entailing the use of dedicated equipment, a separate nurse for each CDAD patient, as well as the use of personal protective equipment like gown, cap, mask, and gloves. Since *C. difficile* spores resist being killed by alcohol, handwashing using soap, and water should be mandatory after contact with every patient. Contact isolation must continue for at least 48 hours after diarrhea has resolved. Surveillance of CDAD is an important aspect of infection control. Incidence of CDAD over time and in different healthcare units/wards should be monitored for timely recognition of clusters or outbreaks. This helps in focused implementation of rigorous infection control measures.

The most important preventive aspect of CDAD is the reduction in antibiotic exposure of patients. Judicious antibiotic therapy practices such as avoiding unnecessary empiric usage, culture guided treatment, timely de-escalation to narrow spectrum antibiotics, avoiding unnecessary long-term usage, and timely termination of treatment need to be followed to decrease the risk of emergence of CDAD. Robust stewardship programs must be enforced and regulated.[33]

Conclusion

CDAD can be associated with significant morbidity and mortality in oncology patients. The diagnosis needs to be made promptly and colonization must be distinguished from infection. Prompt therapy must be initiated; therapeutic options may be limited in the Indian setting. The pros and cons of administering a FMT must be weighed carefully before performing the procedure. Strict infection control protocols need to be enforced. More data are needed from India regarding the unique challenges posed by CDAD in our settings.

Conflict of Interest
None declared.

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Determination of the Quality of Life of Parents with Children Treated in the Pediatric Oncology Clinic during the COVID-19 Pandemic and Affecting Factors

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Abstract

Introduction Even in the absence of a pandemic, pediatric oncology patients have decreased immunological levels. This condition requires families to monitor their children's risk of infection on a frequent basis. The possibility of being exposed to coronavirus disease 2019 (COVID-19) in a hospital or community environment has created significant concern among cancer families.

Objectives This study sought to ascertain the quality of life of parents who sought treatment for their children at a pediatric oncology clinic during the COVID-19 epidemic, as well as the factors that influenced it.

Materials and Methods This cross-sectional study included 62 parents with children ages 0 to 19 who receive treatment for their children at the pediatric oncology clinic of an application and research center in Turkey's Western Black Sea area. "The Participant Information Form" and "The Scale of Quality of Life-Family Version (QOL-FV)" were used to collect data. The researchers used the face-to-face interview approach to obtain data. To investigate the differences in scale levels based on the descriptive characteristics of the parents, one-way analysis of variance, *t*-test, and post hoc (Tukey, least significant difference) analyses were used.

Results The total mean score of the parents' QOL-FV was found to be 148.097 ± 25.843 (87–258). In the study, it was determined that financial difficulties, difficulties in accessing the hospital during the treatment process, and changes in daily activity/behavior had negative effects on parents' quality of life.

Conclusion Most of the parents who participated in our study stated that their quality of life got worse with the pandemic. It was determined that the COVID-19 pandemic had effects on the quality of life of parents of pediatric oncology patients in various ways.

Keywords
- COVID-19
- quality of life
- child
- cancer

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Introduction

The public health measures necessary to reduce viral spread, pose a major threat to children with medical complexity, especially to pediatric oncology patients.[1,2] Childhood cancers are curable when correct diagnosis and appropriate treatment are provided on time.[3] Children with cancer often require long-term intensive chemotherapy.[4] They are at risk for reduced response rates, worsening disease prognosis, and disease relapse due to delays, interruptions, or significant changes in their treatment.[3] Although the real impact of coronavirus disease 2019 (COVID-19) on children undergoing treatment for cancer is still unknown, it is advised that standards of diagnosis, treatment, and supportive care remain unchanged during the pandemic.[4–7]

Pediatric oncology patients have suppressed immune levels even without a pandemic. This condition forces families to regularly manage their children's risk of infection.[8] It is assumed that children with cancer are more susceptible to COVID-19.[9] Virus infections are also linked to higher mortality and morbidity in immunocompromised children.[10] As a result, the potential of COVID-19 exposure in hospital or community settings has created substantial concern among cancer families.[4] It has been determined that parents of pediatric oncology patients face a high psychological risk as a result of COVID-19-induced posttraumatic symptoms, high stress, and anxiety levels.[11] Lack of information about COVID-19, increased precautions due to fear of infection, concerns about the change of treatment and going to hospital, future uncertainty of COVID-19, and its psychosocial and economic impacts negatively influence the quality of life (QOL) of parents.[12,13]

Pediatric oncology nurses are of great importance in coordinating the child's care and identifying their needs.[2] However, the health of the child is closely related to the health of the caregivers as a result of the family-centered approach, which is the most important component of pediatric care.[14] Nurses should consider not only the child's but also the emotional and social needs of the family.[15] Therefore, this study was carried out to examine the QOL of parents whose children were treated in a pediatric oncology clinic during the COVID-19 process and to determine the affecting factors.

Materials and Methods

Design, Population, and Sample

The research is a descriptive study to determine the QOL of parents who applied to the pediatric oncology clinic for the treatment of their children during the COVID-19 pandemic and to determine the affecting factors. The study's population included 62 parents with children aged 0 to 19, were literate and applied to the pediatric oncology clinic of an application and research center in the Western Black Sea region of Turkey between June 1, 2021 and January 1, 2022 for the treatment of their children. Sample selection was not made. Only the universe was studied. Inclusion criteria for family caregivers in the study were as, having a child aged 0 to 19 and receiving cancer treatment, being able to read and write, and having no psychiatric diagnosis. The exclusion criteria were to refuse to participate in the study.

Data Collection Tools

To collect data, the "Participant Information Form" and "The Scale of Quality of Life Family Version (QOL-FV)" were utilized. The researchers collected data using the face-to-face interview approach in the pediatric oncology service of the application and research hospital during working hours between the study periods.

Participant Information Form

Based on the literature, the researchers developed this form, which comprised 45 questions regarding the sociodemographic features of parents and their children, their present disease, and treatment-related status.[12,16]

The Scale of Quality of Life Family Version

The scale developed by Ferrell and Grant was adapted into Turkish by Okçin and Karadakovan.[17,18] Physical health, psychological health, social issues, and spiritual well-being are the four subdimensions of the 37-item measure. The study's test–retest reliability was $r = 0.86$, and the internal consistency Cronbach's alpha value was $r = 0.90$. The scale's scoring ranges from 0 to 10. The total score and subdimension scores are used to interpret the scale, and a high score indicates a high QOL.[18] The Cronbach's alpha value of the scale was found to be 0.817 in our study.

Data Analysis

The research data were analyzed in a computer environment using the SPSS 24.0 statistical program.[19] The frequency and percentage analyses were used to identify the descriptive features of the parents, and the scale was examined using mean and standard deviation statistics. The normal distribution of the research variables was discovered. Parametric approaches were used to examine the data. The links between the dimensions that affect the scale levels of the parents were investigated using correlation and regression analysis. To evaluate variations in scale levels depending on the descriptive features of the parents, *t*-tests, one-way analysis of variance, and post hoc (Tukey and least significant difference) analyses were utilized. The findings were evaluated within a 95% confidence range, with $p < 0.05$ considered significant.

Ethical Considerations

The Human Research Ethics Committee of Zonguldak Bülent Ecevit University granted permission to perform the research (Decision No: 30.04.2021/43431, Protocol no: 191). The institution where the research was conducted provided the necessary institutional permission. Prior to the study, participants were asked to sign informed consent forms. All methods in studies involving human subjects were carried out in line with the institutional and/or national research committee's ethical standards, as well as the 1964 Helsinki Declaration and its subsequent revisions or similar ethical standards.

Results

When the sociodemographic characteristics of the parents constituting the sample of the study were examined, it was determined that 32.3% of the mothers were 35 years old and younger, 32.3% were between 36 and 40 years old, and 35.5% were 40 years old and older. The mothers' educational level was 45.2% high school graduates and 30.6% associate degree graduates. It was determined that 32.3% of the mothers were employed, 67.7% were housewives/retired, and 90.3% did not have a chronic disease. It was found that 17.7% of the fathers of the children were 35 years old and younger, 30.6% were between 36 and 40 years old, and 51.6% were 40 years old and older, 38.7% were university graduates, 98.4% were employed, and 96.8% did not have a chronic disease. It was found that 66.1% of the parents had another child/children at home, 48.4% had a lower income than their expenses, 51.6% had an income equal to their expenses, and 53.2% resided in a district/town, and 12.9% had another patient/elderly dependent at home.

When the sociodemographic characteristics of the children participating in the study were examined, 58.1% were boys, 22.6% were between the ages of 1 and 3, 30.6% were between the ages of 4 and 6, 27.4% were between the ages of 7 and 12, and 19.4% were between the ages of 13 and 18. It was determined that 56.5% of those who cared for a sick child at home were mothers, while 43.5% were parents together. Note that 41.9% of the families did not reside in the same city as the hospital where they were treated, and 67.7% provided transportation by their own vehicle and 12.9% by taxi. Also, 43.5% of the children were under treatment for the diagnosis of acute lymphoblastic leukemia and 59.7% were inpatients.

The distribution of parents according to the COVID-19 pandemic and related problems is given in ►**Table 1**. The QOL-FV mean scores of the parents were found to be 148.097 ± 25.843 (87–258). When the subdimensions of the scale were examined, mean score of "physical health" was determined to be 26.919 ± 7.521 (13–42), "psychological health" 59.871 ± 12.775 (32–107), "social concerns" 61.307 ± 13.388 (39–122), and "spiritual well-being" 6.177 ± 2.207 (2–10) (►**Table 2**).

When the difference between the scores of the QOL-FV according to the sociodemographic characteristics of the parents was examined, the total QOL scores of those who did not have other children ($x = 138.571$) were found to be lower than those who had, and a significant difference was found between them ($p = 0.037 < 0.05$). The social concerns scores of those who did not have other children were found to be lower than those who had ($p = 0.05$). The social concerns ($p = 0.027 < 0.05$) and spiritual well-being ($p = 0.018 < 0.05$) scores of the parents who did not have dependent patients were lower than those of the parents who did. The total QOL-FV ($x = 139.694$) ($p = 0.004 < 0.05$), psychological health ($p = 0.007 < 0.05$), and social concerns ($p = 0.014 < 0.05$) scores of those who did not reside in the same city with the hospital where the treatment took place were higher than those who resided in the same city (►**Table 3**).

Table 1 Distribution of parents by COVID 19 and related problems

Variables	*n*	%
Diagnosis of COVID-19 in child's family		
No	43	69.4
Yes	19	30.6
Experiencing financial difficulty due to COVID-19		
No	14	22.6
Yes	48	77.4
Having challenges in the treatment of the child due to COVID-19		
No	18	29.0
Yes	44	71.0
Delay/cancellation of the child's checkup appointments due to COVID-19		
No	46	74.2
Yes	16	25.8
Change/Cancellation in child's treatment due to COVID-19		
No	52	83.9
Yes	10	16.1
Transportation difficulties due to COVID-19		
No	29	46.8
Yes	33	53.2
Inability to access medicine due to COVID-19		
No	61	98.4
Yes	1	1.6
Behavior changes in parents due to COVID-19		
No	34	54.8
Yes	28	45.2
Daily activity changes in parents due to COVID-19		
No	34	54.8
Yes	28	45.2
Thinking that the pandemic process affected quality of life		
My quality of life did not change.	23	37.1
My quality of life got worse with the pandemic.	39	62.9
Total	62	100.0

Abbreviation: COVID-19, coronavirus disease 2019.

In the study, when the scores of the QOL-FV were examined according to the descriptive characteristics of the child and treatment methods, the physical health score of girls were lower than that of boys ($p = 0.005 < 0.05$). The physical health scores of the outpatients were higher than those of the inpatients ($p = 0.003 < 0.05$) (►**Table 4**).

QOL-FV of children with COVID-19 in the family was found to be lower than that of children without a COVID-19 diagnosis at home ($p = 0.028 < 0.05$). The social concerns ratings of individuals without a COVID-19

Table 2 The scale of the Quality of Life Family Version (QOL-FV) mean scores of the parents

	n	Mean	SD	Minimum	Maximum
Scale total score mean	62	148.097	25.843	87	258
Subdimensions					
Physical health	62	26.919	7.521	13	42
Psychological health	62	59.871	12.775	32	107
Social concerns	62	61.307	13.388	39	122
Spiritual well-being	62	6.177	2.207	2	10

Table 3 Variation of the Quality of Life Family Version (QOL-FV) scores of parents by sociodemographic characteristics

Variables	*n*	Quality of life total mean ± SD	Physical health mean ± SD	Psychological health mean ± SD	Social concerns mean ± SD	Spiritual well-being mean ± SD
Presence of other children at home						
No	21	138.571 ± 22.342	24.810 ± 6.824	57.095 ± 12.930	56.667 ± 10.047	5.667 ± 2.153
Yes	41	152.976 ± 26.398	28.000 ± 7.710	61.293 ± 12.616	63.683 ± 14.345	6.439 ± 2.214
t		−2.137	−1.601	−1.230	−2.000	−1.312
p		**0.037**	0.115	0.224	**0.050**	0.195
Family income						
Income is less than expenses	30	142.900 ± 16.612	25.767 ± 7.408	58.400 ± 10.371	58.733 ± 7.710	6.433 ± 1.832
Income is equal to expenses	32	152.969 ± 31.708	28.000 ± 7.582	61.250 ± 14.712	63.719 ± 16.872	5.938 ± 2.514
t		−1.551	−1.172	−0.876	−1.480	0.883
p		0.121	0.246	0.384	0.144	0.376
Presence of other patients/elderly dependent						
No	54	146.241 ± 23.081	27.241 ± 7.658	59.130 ± 11.845	59.870 ± 11.380	5.926 ± 2.171
Yes	8	160.625 ± 39.756	24.750 ± 6.541	64.875 ± 18.083	71.000 ± 21.401	7.875 ± 1.727
t		−1.484	0.872	−1.191	−2.268	−2.423
p		0.143	0.386	0.238	**0.027**	**0.018**
Residing in the same city as the hospital where the treatment took place						
No	26	159.731 ± 29.749	28.654 ± 7.761	64.923 ± 14.910	66.154 ± 15.470	6.615 ± 2.246
Yes	36	139.694 ± 18.939	25.667 ± 7.191	56.222 ± 9.643	57.806 ± 10.553	5.861 ± 2.153
t		3.238	1.561	2.790	2.528	1.337
p		**0.004**	0.124	**0.007**	**0.014**	0.186

Abbreviation: SD, standard deviation.
($p<0.05$)

diagnosis at home were found to be lower than those with a COVID-19 diagnosis at home ($p = 0.034 < 0.05$). When the score of experiencing financial difficulties due to COVID-19 were compared with the scale scores, the total QOL-FV scores ($p = 0.008 < 0.05$), psychological health scores ($p = 0.014 < 0.05$), and social concerns scores ($p = 0.029 < 0.05$) of families who did not experience financial difficulties due to COVID-19 were found to be higher than those who did. Social anxiety scores of parents who thought that their QOL did not change were found to be higher than those who did not ($p = 0.02 < 0.05$) (►**Table 5**).

Discussion

Cancer is a complicated and sometimes fatal disease that affects many parts of life and exposes patients and their families to a wide range of psychological and health-related issues.[20] The COVID-19 pandemic has a wide variety of consequences for parents who care for children with cancer.[11,21,22] Compared to the studies in the pre-pandemic period, it was observed that the QOL-FV total scores of the parents who constituted the sample of our study were higher.[23,24] However, the total QOL-FV scores of the parents in our study were found to be below the

Table 4 Variation of the Quality of Life Family Version (QOL-FV) scores according to children's descriptive characteristics and treatment types

Variables	*n*	Quality of life total mean ± SD	Physical health mean ± SD	Psychological health mean ± SD	Social concerns mean ± SD	Spiritual well-being mean ± SD
Age						
1–3 y	14	143.214 ± 22.461	23.214 ± 9.545	59.643 ± 12.616	60.357 ± 7.841	5.500 ± 2.175
4–6 y	19	141.632 ± 23.966	26.895 ± 5.980	56.421 ± 12.764	58.316 ± 13.246	5.947 ± 2.272
7–12 y	17	153.882 ± 22.613	29.294 ± 7.856	62.471 ± 10.736	62.118 ± 12.108	6.765 ± 1.678
13–18 y	12	155.833 ± 34.701	27.917 ± 5.518	61.917 ± 15.716	66.000 ± 19.475	6.500 ± 2.747
t		1.218	1.841	0.792	0.845	0.995
p		0.311	0.150	0.503	0.475	0.402
Gender						
Girl	26	145.039 ± 31.041	23.615 ± 8.280	59.115 ± 15.050	62.308 ± 15.041	6.346 ± 2.244
Boy	36	150.306 ± 21.535	29.306 ± 5.971	60.417 ± 11.041	60.583 ± 12.227	6.056 ± 2.203
t		−0.789	−3.147	−0.393	0.497	0.509
p		0.433	**0.005**	0.696	0.621	0.613
Treatment type						
Outpatient	25	150.200 ± 18.385	30.240 ± 6.064	60.840 ± 11.564	59.120 ± 7.775	6.680 ± 1.994
Inpatient	37	146.676 ± 30.019	24.676 ± 7.649	59.216 ± 13.649	62.784 ± 16.057	5.838 ± 2.304
t		0.524	3.045	0.488	−1.058	1.489
p		0.602	**0.003**	0.627	0.294	0.142
Number of course treatment						
4 times and less	34	144.941 ± 26.122	26.088 ± 6.690	59.059 ± 12.964	59.794 ± 13.984	5.794 ± 2.422
5 times and more	28	151.929 ± 25.438	27.929 ± 8.437	60.857 ± 12.707	63.143 ± 12.631	6.643 ± 1.850
t		−1.061	−0.958	−0.548	−0.980	−1.523
p		0.293	0.342	0.585	0.331	0.133
Presence of another chronic disease						
No	59	148.441 ± 25.933	27.034 ± 7.536	59.780 ± 12.457	61.627 ± 13.604	6.203 ± 2.211
Yes	3	141.333 ± 28.184	24.667 ± 8.387	61.667 ± 21.733	55.000 ± 6.083	5.667 ± 2.517
t		0.462	0.529	−0.248	0.834	0.408
p		0.646	0.599	0.805	0.407	0.685

Abbreviation: SD, standard deviation.
($p<0.05$)

average. Approximately two-thirds of the parents participating in our study stated that their QOL got worse with the pandemic, and our results indicated that various factors during the COVID-19 pandemic period had effects on the QOL of families who had a child with cancer.

In the study, it was found that the QOL-FV score of parents with a family history of COVID-19 was surprisingly high compared to those without a family diagnosis of COVID-19. It is thought that this result may be coincidental or may be due to the difference in the methods of families coping with the disease.

In studies conducted before the pandemic and during the pandemic, it was revealed that parents with a child with cancer experienced financial difficulties.[8,25–29] None of the parents in our study stated that their income was more than their expenses, and it was observed that the QOL of families whose income was less than their expenses was already lower. In a study conducted with mothers of children with leukemia, it was found that mothers quitted their jobs in order not to transmit infection to their children, which led to economic difficulties, and therefore they had difficulty in taking their children to the hospital (finding a vehicle, etc.).[25] In the study conducted by Wimberly et al, 9% of caregivers of children receiving pediatric oncology treatment reported that they had transportation difficulties in order to arrive at their appointments on time.[12] In our study, it was observed that more than half of the parents (53.2%) had difficulties with transportation. Therefore, it is possible to say that the problem of transportation to the treatment center, which is closely related to financial difficulties, negatively affects the QOL of parents who have children receiving pediatric oncology treatment during the COVID-19

Table 5 Variation of the Quality of Life Family Version (QOL-FV) scores according to the problems families experienced due to COVID-19

Variables	*n*	Quality of life total mean ± SD	Physical health mean ± SD	Psychological health mean ± SD	Social concerns mean ± SD	Spiritual well-being mean ± SD
Diagnosis of COVID-19 in the child's family						
No	43	143.349 ± 21.372	25.698 ± 7.186	58.721 ± 11.348	58.930 ± 10.003	5.977 ± 2.241
Yes	19	158.842 ± 31.966	29.684 ± 7.718	62.474 ± 15.565	66.684 ± 18.163	6.632 ± 2.114
t		−2.247	−1.969	−1.068	−2.165	−1.079
p		**0.028**	0.054	0.290	**0.034**	0.285
Experiencing financial difficulty due to COVID-19						
No	14	164.000 ± 34.331	25.286 ± 6.888	67.143 ± 14.507	71.571 ± 19.848	6.571 ± 1.910
Yes	48	143.458 ± 21.059	27.396 ± 7.698	57.750 ± 11.544	58.313 ± 9.117	6.063 ± 2.292
t		2.755	−0.923	2.525	3.559	0.757
p		**0.008**	0.360	**0.014**	**0.029**	0.452
Having difficulty in the treatment of the child due to COVID-19						
No	18	152.333 ± 22.562	26.500 ± 8.515	61.778 ± 10.514	64.056 ± 13.050	5.833 ± 1.978
Yes	44	146.364 ± 27.122	27.091 ± 7.175	59.091 ± 13.626	60.182 ± 13.508	6.318 ± 2.300
t		0.823	−0.279	0.749	1.035	−0.783
p		0.414	0.781	0.457	0.305	0.437
Behavioral changes in parents due to COVID-19						
No	34	147.853 ± 21.545	26.059 ± 8.431	60.294 ± 10.182	61.500 ± 11.657	6.177 ± 1.914
Yes	28	148.393 ± 30.682	27.964 ± 6.233	59.357 ± 15.540	61.071 ± 15.451	6.179 ± 2.554
t		−0.081	−0.993	0.285	0.124	−0.004
p		0.936	0.311	0.776	0.901	0.997
Daily activity changes in parents due to COVID-19						
No	34	151.677 ± 28.355	26.765 ± 7.636	61.853 ± 12.943	63.059 ± 15.807	6.206 ± 2.115
Yes	28	143.750 ± 22.147	27.107 ± 7.515	57.464 ± 12.369	59.179 ± 9.538	6.143 ± 2.353
t		1.206	−0.177	1.355	1.138	0.111
p		0.232	0.860	0.180	0.259	0.912
Thinking that the pandemic process affected quality of life						
My quality of life did not change	23	153.739 ± 19.610	24.783 ± 8.107	62.565 ± 9.024	66.391 ± 11.011	6.304 ± 2.032
My quality of life got worse with the pandemic	39	144.769 ± 28.615	28.180 ± 6.954	58.282 ± 14.417	58.308 ± 13.879	6.103 ± 2.326
t		1.328	−1.747	1.282	2.383	0.345
p		0.189	0.086	0.205	**0.020**	0.731

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation.
($p<0.05$)

period. However, in our study, it is surprising that the total QOL of parents who did not reside in the same city with the hospital where the child was treated was higher than those who did.

As COVID-19 cases increased and governments implemented stay-at-home measures, applications to the hospital for treatment decreased significantly, and children were undoubtedly the population most affected by this situation caused by COVID-19.[30] In a study conducted in the United States, 26% of caregivers reported delay/cancellation in their pediatric oncology appointments during the pandemic.[12] In our study, although the rate of delay/cancellation of control appointments (25.8%) was quite consistent with the study of Wimberly et al, the QOL of parents who had difficulties in the treatment process due to COVID-19 was found to be lower.[12]

Even if there is no pandemic, parents of cancer children must constantly monitor their child's infection risk.[8] Patients are at risk of getting several infectious infections due to the immunosuppressive effect of cancer and accompanying therapies.[31] Prior to the commencement of the pandemic, parents who participated in the Steinberg et al study said that their daily lives were packed with routines, and once

COVID-19 cases arose, they felt obliged to make modifications in their children's daily routines to safeguard them due to their medical issues.[32] Additional variables, including as social distance and new daily behaviors adopted by parents of pediatric cancer patients as a result of COVID-19, were found to have a significant influence on parents' QOL in other research.[11,33] In line with the literature, our findings suggested that daily activity and behavioral changes caused by COVID-19 had a detrimental impact on parents' QOL.

Limitations

This research has some methodological limitations. Since all the data were collected during the pandemic period, a comparison with the same participants before the pandemic could not be made. We compared our study with other studies conducted before the pandemic. In addition, the results are limited to the sample group, clinic, and date in which the research was conducted.

Conclusion

The main findings of this study show that the COVID-19 epidemic has negative consequences on the QOL of parents of pediatric cancer patients. An examination of these issues offers a fresh perspective on how to improve parents' QOL during challenging times. The COVID-19 pandemic has had a substantial effect on pediatric cancer care, presenting an unprecedented global threat to the safe and effective care of children with cancer. More studies are required to quantify these challenges and to develop solutions that relieve the stress and suffering of those children and their families. With the outbreak of the COVID-19 epidemic, nurses have taken on increased obligations to ensure that parents spend this time with little physical and psychological harm.

Ethical Considerations

The Human Research Ethics Committee of Zonguldak Bülent Ecevit University granted permission to perform the research (Decision No: 30.04.2021/43431, Protocol no: 191). The institution where the research was conducted provided the necessary institutional permission. Prior to the study, participants were asked to sign informed consent forms. All methods in studies involving human subjects were carried out in line with the institutional and/or national research committee's ethical standards, as well as the 1964 Helsinki Declaration and its subsequent revisions or similar ethical standards.

Authors' Contributions

Concept: A.T., Z.A., Ö.Ö.Ş.; Design: A.T., Ö.Ö.Ş.; Literature search: A.T., Z.A.; Data acquisition: D.B., T.K.A.; Statistical analysis: A.T., Z.A., T.K.A.; Manuscript preparation: A.T., Z.A.; Manuscript editing: A.T., Z.A., Ö.Ö.Ş.; Manuscript review: Ö.Ö.Ş., T.K.A.

Data Availability Statement

Data available on request from the authors.

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Conflict of Interest

None declared.

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Expected Usefulness of Fourth Dose of COVID-19 Vaccine for Patients with Underlying Solid Tumor who Previously Received the Primary Heterologous COVID-19 Vaccine

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Abstract

Coronavirus disease 2019 (COVID-19) immunization frequently requires two standard doses. Due to the likelihood that the population may lose immunity after receiving a standard mass vaccination and the potential for the introduction of a new strain, several scientists are currently advocating the use of a booster dosage of the vaccine. The authors of this retrospective study used a clinical model for immune response prediction to forecast how solid cancer patients will respond to the fourth dosage of the COVID-19 immunization. In the case of homologous primary backgrounds, the prospective rates of extension of protective efficacy for using viral vector and messenger ribonucleic acid (mRNA) COVID-19 vaccines for vaccinees with underlying solid tumor are equal to 11.5 and 16.5%, respectively. In the event of heterologous primary backgrounds, the prospective rates of extension of protective efficacy for using viral vector and mRNA COVID-19 vaccines are equal to 2.2 and 7.2%, respectively, for patients with underlying solid cancer. In conclusion, the fourth dose of the COVID-19 vaccine regimen had an effect on the immunogenicity of vaccine recipients with underlying malignancy.

Keywords
- COVID-19
- dose
- fourth
- vaccine
- cancer

Introduction

Coronavirus disease 2019 (COVID-19) has affected the entire world.[1] Vaccination is the finest disaster management strategy.[2] Traditionally, two vaccination doses are required for complete immunization. Several experts advise administering an additional COVID-19 booster dose when there is an emerging variant and a possible drop in protective immunity occurs after a normal vaccine administration.[3–5]

After vaccination, antibody levels may drop, necessitating practice to prevent infection. The effectiveness of the COVID-19 vaccine in certain populations of vaccine recipients with background personal illnesses is a significant clinical problem. Immune responses to standard immunizations are poor in immunocompromised people and those with problematic autoimmunity (such as lupus and cancer).[1] Patients with compromised immune systems are at a higher risk of developing significant vaccine resistance.[1] Despite the fact that many people are still concerned, the third and second COVID-19 vaccination doses are occasionally used as booster doses. The additional dose of COVID-19 vaccine is on its way, and the next injection is already planned.

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Some scientists advocate for an additional vaccination dose in the event of the emergence of a new type of pathogen as well as the anticipated loss of public immunity after regular mass immunization. Because the efficacy of the additional dosage of the COVID-19 vaccine is unknown, any research into its efficacy is intriguing. The third dosage of the vaccination for patients who have malignancy is the topic for further discussion right now in clinical oncology.[6–11] According to some recent clinical trial findings,[12–15] the third vaccination dose may be beneficial. Increased immunity is usually observed after the third dose immunization, and there is no significant increase in the incidence of postvaccination adverse events.[12–15] Those studies, however, are frequently based on a small number of participants and focus on a specific COVID-19 vaccine type. The impact of confounding variables, such as previous asymptomatic COVID-19, is typically not excluded in those studies.[12–17] Those who have had the recommended vaccinations are also becoming ill as a result of the unusual pathogen strain.

Adding to the third dose of the basic vaccine, several countries, particularly those with a history of nonstandard heterologous vaccination for the first and second doses, are still dealing with an uncontrolled COVID-19 outbreak. A third vaccine is already in use, but an additional booster is still required. Many countries, including those in Southeast Asia, have already declared and implemented the additional fourth dose policy. The precise efficacy of the fourth dose vaccine is an intriguing issue that has received little attention. The data on subjects with underlying diseases, such as solid tumors, is also extremely limited. Cancer patients will be given the fourth dose of the COVID-19 vaccine here, and the researchers will use a clinical model to predict how they will react.

Materials and Methods

Study Design

The response of cancer patients to the fourth dose of the COVID-19 vaccine was predicted by the researchers using a clinical model. The emphasis is concentrated on mathematical model application in medicine. The method is a typical in silico mathematical modeling tool that is unaffected by complex environmental variables, according to an in vitro and in vivo evaluation. "Primary data"[18] refers to the fundamental data regarding the infection protection effectiveness rates of different types of vaccine. It is crucial to understand that each vaccination has a different immunogenicity mechanism. Vaccines made with various biotechnologies comprise a wide range of necessary components, resulting in a wide range of immunoprotection inductions. Following routine immunization, the maximal level of infection protection efficacy, or effective immune response, will be derived. The immune system's effectiveness will rise with the addition of the dose.

Assessment of a Booster Dose of a Vaccination

Mathematical modeling is used to assess the efficacy of a booster vaccination.[19] The current study is retrospective in nature and uses a mathematical model method. Human test subjects are not required for the evaluation of a novel vaccine whose safety has not yet been established, according to the procedure described for evaluating vaccine efficacy in silico.[19] According to in vitro and in vivo studies, mathematical modeling can generate a reasonable prediction result without the influence of environmental confounding factors.[19]

The arithmetic mathematical model is used in this study to evaluate a booster dose of a vaccination. The model is static and linear in structure. Data that was previously accessible is used as the model's main input. The impact of a booster was examined in a prior clinical experiment that employed the same modeling strategies as this one. The protective effectiveness following the booster dose will probably be regarded as background infection protection efficacy for modeling purposes. When administered as a booster dosage, the additional dose may raise the protective efficacy rate and boostering activity, but it would not exceed the baseline protective efficacy rate. Contrary to popular belief, the background protective efficacy of the booster immunization will not be greater than the ultimate protective efficacy. According to the previously indicated calculation, the final projected infection protection efficacy rate after the fourth dose will be computed as "background protective effect after the third dose + additional protection from the fourth dose." This model can be used to forecast the immune response to the fourth booster vaccine in vaccine recipients with a baseline solid tumor. The model can be run using straightforward arithmetic operations. The model's mathematical methodology allows for the elimination of biological confounding variables.

This model simulates and forecasts the action of the fourth dosage of the COVID-19 vaccination using fundamental data from a developing Asian nation with a problem of highly endemic, uncontrollable infection.

Background: Some individuals in this condition received two heterologous COVID-19 shots in addition to two booster doses of the vaccine. An inactivated-inactivated, messenger ribonucleic acid (mRNA) viral vector is often utilized for the fundamental doses of the COVID-19 vaccination (https://www.prachachat.net/marketing/news-837033). In brief, in this setting, the primary backgrounds, the first and second doses, are either inactivated vaccine and inactivated vaccine, which is called homologous path, or inactivated vaccine plus viral vaccine, which is called the heterologous path. The third dose is generally an mRNA vaccine. The following modeling study is based on the most recent publicly available data on the protection ability of the third booster. Utilizing earlier data on the immunization's effectiveness in cancer cases, changes to the vaccine's reported efficacy are also made.[20]

The model was developed using a retrospective analysis of clinical data that was made available to the public. Therefore, there are no confounding factors in the effectiveness analysis of the current study. Additionally, there are no human or animal subjects, and therefore informed consent or ethical approval is not required. As discussed earlier, a mathematical model can be developed and used to predict how the fourth

dose of the immunization will affect young people who are at risk for developing cancer.

Primary and Secondary Outcome

The primary outcome in this study is the predicted protection rate after the fourth dose. The secondary outcome is the possible expansion of protective efficacy.

Inclusion and Exclusion Criteria

In the present clinical mathematical model study, the purposive inclusion is done in order to get the primary data for further simulation, as earlier mentioned. In the event that there is no complete data, an exclusion is set.

Statistical Analysis

Basic mathematics and descriptive statistics are employed in this investigation. A percentage calculation serves as the foundation for the direct arithmetic computation. The estimate of a potential growth of preventive efficacy is based on the mathematical model, which uses arithmetic subtraction. "Possible expansion of protective efficacy" is calculated using the formula "Expected greatest protective efficacy rate after the fourth dose – Background protective effect after the third dose."

Ethics

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study is a clinical mathematical model study and does not directly deal with patients, and therefore, ethical approval is not applicable, and the consent form is also not applicable.

Results

Protection Rare after the Fourth Dose

A clinical model study indicates that varied fourth dosage regimens can provide varying protection rates, which is according to varying projected infection protection efficacy for various background immunizations (►**Table 1**). Vaccination recipients with underlying solid tumors may experience altered immune responses to all vaccine kinds. The greatest protective efficacy rates for the viral vector and mRNA COVID-19 in cases with homologous primary backgrounds are predicted to be 89% and 94%, respectively, after the fourth immunization. The greatest protective efficacy rates for the viral vector and mRNA vaccines in cases with heterologous primary backgrounds are anticipated to be 89 and 94%, respectively, following the fourth immunization.

Possible Expansion of Protective Efficacy

Compared to the viral vector vaccine, the mRNA COVID-19 can more effectively stimulate the immune system. The prospective rates of expansion of protective efficacy for using viral vector and mRNA vaccines are examined for recipients with underlying solid tumors.

The background protection impact after the third dose and the expected viral vector vaccine's maximal protective efficacy rate are equal to 77.5 and 89% in the case of homologous primary backgrounds, respectively. As a result, 11.5% is the theoretical rate of protective effectiveness extension. The mRNA vaccine's highest anticipated protective efficacy rate is predicted to be 94%, with a background protective effect of 77.5% following the third dose. As a result, 16.5% is the potential rate of protective effectiveness extension.

The background protection impact after the third booster and the expected maximal protective efficacy rate for the viral vector vaccine for the case with heterologous main backgrounds are equivalent to 86.7 and 89%, respectively. As a result, 2.2% will be the theoretical rate of protective efficacy extension. The mRNA vaccine's highest anticipated protective efficacy rate is predicted to be 94%, with a background protective effect of 62.34% following the second vaccine administration. The potential rate of infection protection efficacy extension is expected to be 7.2%.

Table 1 Expected immunoprotection after the fourth dose of COVID-19 vaccine for cases with underlying cancer

The fourth dose vaccine		Protective efficacy rate (%)				
Type	Specific boostering[a] activity (%)	Background protective effect after the third dose[b] (%)		Expected highest protective efficacy rate after the fourth dose (%)	Possible expansion of protective efficacy (%)	
		Homologous Primary background[c]	Heterologous primary background[c]		Homologous Primary background	Heterologous primary background
Viral vector	35.9	77.5	86.7	89	11.5	2.2
mRNA	23.3	77.5	86.7	94	16.5	7.2

Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid.
[a]If a vaccine is given as a second dose, a certain booster activity can increase the protective efficacy rate of the first dose.
[b]The background protective effect following the second dose of the vaccine is the immunoprotection rate, and data are based on an open report from a developing Southeast Asian country.[19]
[c]Primary background in the setting: homologous = inactivated + inactivated vaccine + mRNA vaccine, heterologous = inactivated + viral vector + mRNA vaccine.

Discussion

Even after receiving both doses of the vaccine, a coronavirus infection is still possible, so preventive action is essential. Additionally, for some vaccine recipients, protection is limited after two vaccine doses. As a result, booster vaccine doses have been recommended and are being given in a variety of situations. Few studies have looked into the efficacy of the subsequent booster, with a majority focusing on immune-compromised populations. Many experts now agree that a vaccine booster dose can improve immune responses, though it is not always necessary.[3–5]

Due to an inability to control the disease, some regions, particularly those in Indochina, historically used a second dose of the immunization. Individuals with cancer are also among those receiving the second boost.[20] The vaccination's effectiveness is still being debated after the second dose. Because the developed immunity is still modest, a third dose is recommended.

In immunocompromised individuals, further COVID-19 immunization is commonly administered to strengthen immunity and guard against the constantly evolving COVID-19 variation.[3–5] Some regions, especially those in Indochina, historically required a second dose of the vaccine since the sickness was uncontrollable. Patients with cancer are recommended for boosters as well.[8] After the second dose, there is still disagreement on the vaccine's efficacy. A fourth dose is advised because the already-established immunity is still underwhelming. Many healthy individuals have already received an additional dose of the vaccine since the first and second doses were of poor quality. Current best practices recommend booster whenever an underlying illness is present. The primary COVID-19 prevention method for the population of cancer patients should, in accordance with the Centers for Disease Control and Prevention's recommendations, be immunization. It can demonstrate that in subjects with preexisting malignancies, the booster COVID-19 vaccination dosage can still offer additional immunoprotection. There is an immunological gap that the additional dose of vaccine may fill because the background immunization in this situation does not follow the regular mRNA vaccine schedule.

The predicted immunoprotection after the fourth dosage may differ in patients with hybrid immunity, particularly those with a history of past COVID-19 infection and heterologous immunization, due to a variety of circumstances. Individuals with hybrid immunity may have a higher and more robust immune response after getting the fourth dose of the vaccination. The combination of spontaneous infection and subsequent heterologous vaccination may result in a more diversified and comprehensive immune response, including both cellular and humoral immunity. Previous research has found that individuals with hybrid immunity have higher levels of neutralizing antibodies than those with only spontaneous infection or vaccination. As a result, it is reasonable to believe that following the fourth treatment, patients with hybrid immunity will have increased antibody levels, perhaps giving an additional layer of protection against COVID-19. Another theory is that those with hybrid immunity have a longer immunological memory response. The combination of prior infection and subsequent vaccination may result in a more persistent and long-lasting immunological memory, resulting in long-term protection against COVID-19 even after the fourth dosage. Natural infection combined with heterologous vaccination may result in a more diversified antibody repertoire that can better recognize and neutralize variant strains. It should be noted that these are hypothetical notions that would necessitate additional study and clinical trials to determine the real immunoprotection offered by the fourth vaccine dosage in patients with hybrid immunity.

The authors state that the current study can offer crucial data for clinical oncology planning for immunization. The ability of cancer cases to establish immunity against severe acute respiratory syndrome coronavirus 2 has been found to be enhanced by receiving a third dosage of the vaccine, according the current study.[8] Consideration should be given to the mRNA vaccine, which among a variety of vaccine types has the best immunogenicity. The booster immunization using the mRNA vaccine should be helpful in terms of preventive oncology given the current state of the outbreak and the future guidelines on immunizing a patient with an underlying cancer.

Conclusion

In this study, the immunogenicity of vaccinees with an underlying solid malignancy was found to be impacted by the fourth dose of the vaccine. There are several choices to think about if a fourth dose is scheduled.

Patient Consent

This study is a clinical mathematical model study and does not directly deal with patients, and therefore, ethical approval is not applicable, and the consent form is also not applicable.

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Conflict of Interest

None declared.

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Insulinoma-Associated Protein 1 (INSM1) Expression in Neuroendocrine Neoplasms: A Newly Discovered Diagnostic Marker

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Abstract

Introduction Neuroendocrine neoplasms (NENs) are heterogeneous group of neoplasms with relatively low incidence. Diagnosis of NENs requires an integrated approach of histology, immunohistochemistry, and molecular study. In the present study, we evaluated insulinoma-associated protein 1 (INSM1) expression in NENs and correlated it with other established neuroendocrine markers.

Materials and Method Retrospective cross-sectional study was conducted in a tertiary care center. Consecutively, 100 cases from year November 2019 to January 2021 were enrolled in the study and all relevant data were noted.

Results The mean (±standard deviation) age of the patients was 55.5 (±10.6) years with a male preponderance. Total 59% of the tumors were located in the lung of which 67% were poorly differentiated neuroendocrine carcinoma. INSM1 were positive in 97% cases, while synaptophysin (SYN) in 96% and chromogranin A (CgA) in 86%. Correlation of INSM1 expression with SYN and CgA was statistically significant (p-value < 0.05). Mean H-score of INSM1 was significantly higher than SYN and CgA and it was statistically significant (p-value < 0.001).

Conclusion In the present study, the expression of INSM1 was seen in 97% cases of NENs. A statistically significant association was found between INSM1 and traditional NE markers. As a nuclear marker it is easy to interpret and it showed higher H-score. We conclude that INSM1 is a highly sensitive marker and recommend to incorporate it in the routine practice to aid in the diagnostic workup. However, a larger cohort is required to establish the organ-specific sensitivity and specificity of INSM1.

Keywords
- neuroendocrine neoplasms
- insulinoma-associated protein 1
- immunohistochemistry
- traditional neuroendocrine markers
- H-score

Introduction

Neuroendocrine neoplasms (NENs) are heterogeneous group of disorders with varied histological patterns and nomenclature.[1] Recently, the incidence of NENs has been increased from an estimated 1.09 per 100,000 people in 1973 to 6.98 per 100,000 people in 2012 in the United States.[2] According to the Surveillance, Epidemiology, and End Results[3] and Indian[4] data more than 60% of neuroendocrine tumors (NETs) arise from the gastroenteropancreatic NETs (GEP-NETs). Clinical course of NENs is different and depends upon the location of the tumor; however, a significant number of patients can present with advanced stage.[5] All NENs share a common neuroendocrine origin and have varied organ-specific characteristics, biological behavior, prognosis, and treatment.[5] Diagnosis of NENs requires an

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integrated approach of pathological, immunohistochemical, genetic, and molecular markers.[5]

Insulinoma-associated protein 1 (INSM1) is a zinc-finger transcription factor which has a key role in the development of neuroendocrine differentiation in various tissues.[6] Insulinoma-associated-1gene encodes the INSM1, which was first discovered in 1992 at the National Institutes of Health (Bethesda, Maryland, United States) in human pancreatic insulinoma tissue and murine insulinoma cell lines.[7] Rosenbaum et al[8] reported, INSM1 as a robust immunohistochemical marker of neuroendocrine differentiation in normal and neoplastic human tissue. INSM1 is the first and the most widely validated pan-neuroendocrine marker which shows nuclear positivity.

There is a paucity of Indian literature on this new and emerging marker. In the present study, we will investigate the expression of INSM1 in NENs and compare it with the already established neuroendocrine markers.

Materials and Methods

Sample size and study design: This was a retrospective cross-sectional study done at the department of oncopathology in a tertiary cancer center. Consecutive 100 cases of confirmed NENs from November 2019 to January 2021 were enrolled in the study.

Inclusion and exclusion criteria: Immunohistochemically proven cases of NENs were included in the study. Tumors showing neuroendocrine differentiation without immunohistochemical confirmation and inadequate tissue, suspicious lesions, and cytologically diagnosed cases were excluded.

Demographic details were retrieved from the hospital database. All tissues were fixed in 10% buffered formalin and processed for hematoxylin and eosin and immunohistochemical study. NENs are classified according to the World Health Organization classification.[9] Immunostaining using synaptophysin (SYN) (SP11, monoclonal antibody, Thermoscientific, 1:50), chromogranin A (CgA) (LK2H10, monoclonal antibody, Thermoscientific, 1:100), and INSM1 (clone: MRQ-70, rabbit monoclonal antibody, Cell Marque, 1:50) antibodies were done on all cases. Nuclear immunoreactivity for INSM1 and cytoplasmic stain for SYN and CgA in tumor cells were considered positive. For all markers, both the percentage of cells and intensity of immunoreactivity were noted. H-score assessment was done for INSM1, SYN, and CgA.[10–12]

Statistical Analysis

Age, sex, location of tumor, histologic type, and histological grade were noted. Associations between categorical variables (location of tumor, tumor subtype, tumor grade) were analyzed using chi-square test. Wilcoxon rank test was used for comparison of H-score value. Two-sided *p*-values of < 0.05 were considered significant. All statistical analyses were carried out using SPSS 20.

Ethics: The institutional review committee of the Gujarat Cancer and Research Institute approved the study, approval number IRC/35/2019 and date November 14, 2019. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 1 Clinicopathological and immunohistochemical characteristics

Parameters	Number of cases ($n = 100$)
Age	
< 50 y	33
≥ 50 y	67
Site	
Lung	59
GIT + pancreas	31
Others	10
Sex	
Male	81
Female	19
Types	
NET	29
NEC	67
Combined	4
Subtypes	
NET	
NET 1	16
NET2	5
NET3	8
MINEN	1
NEC	
SMCC	65
LCNEC	2
Combined	3
Immunohistochemistry	
Synaptophysin	
Positive	96
Negative	04
Chromogranin	
Positive	86
Negative	14
INSM1	
Positive	97
Negative	03

Abbreviations: GIT, gastrointestinal tract; INSM1, insulinoma-associated protein 1; LCNEC, large cell neuroendocrine carcinoma; MINEN, mixed neuroendocrine nonneuroendocrine neoplasms; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; SMCC, small cell carcinoma.

Results

Clinicohistopathological and immunohistochemical characteristics are described in ►**Table 1**. The mean (±standard deviation [SD]) age was 55.5 (±10.61) years ranging from 25 to 76 years with most of the cases between 51 and 60 years (37%). Male preponderance was noted with male-to-female ratio of 4.2:1. Lung was the most frequently affected organ (59%). Total 67% cases had poorly differentiated neuroendocrine carcinoma (PD-NEC) of which 65% had small cell morphology. Total 43% of cases had a maximum tumor size of > 7 cm. Total 97 cases were positive for INSM1. Of three negative cases, two were PD-NEC of the lung and one was jejunum well-differentiated NET. Of these three negative INSM1 cases, one case was positive for both SYN and CgA, while two were positive of SYN and CgA, respectively.

Correlation of Expression of INSM1 with Tumor Characteristics

Association between various variables is described in ►**Table 2**. INSM1 expression was compared with size, site, histological type, histological grade, histological subtypes, and immunohistochemical markers. Statistically significant association was found between the expression of INSM1 and SYN and CgA (p-value < 0.05). However, no statistically significant association was found between histological type, histological grade, and histological subtypes (p-value > 0.05). Comparison of INSM1 with traditional NE markers is shown in ►**Supp. Figs. S1** and **S2**.

Comparisons of H-Scores

Detailed site-specific H-score calculation for all three antibodies is discussed in ►**Table 3**. Minimum and maximum H-score for all three antibodies was 0 and 300, respectively. Mean (±SD) H-score of SYN, CgA, and INSM1 was 119.65 (±78.706), 108.70 (±99.307), and 194.55 (77.818), respectively. Comparison of H-score is described in ►**Table 4**.

Discussion

NET is a relatively rare disorder and its diagnosis requires an integrated approach. Well-established neuroendocrine markers such as SYN, CgA, and CD56 are cytoplasmic markers and it is difficult to interpret them in small biopsy. In our study, we have evaluated the newly evolved marker INSM1 and compared it with various parameters which are statistically not significant. Our findings are concordant with McHugh et al.[13] In their study they have compared INSM1 in GEP-NENs. Total 97% cases were positive for INSM1, which was higher than the traditional NE markers. Correlation of expression of INSM1 with SYN and CgA showed statistically significant association in our study (p-value < 0.05). Rooper et al[14] studied INSM1 in all thoracic NETs and they have found statistically significant association of INSM1 with SYN and CgA (p-value < 0.001), which was concordant with our study. However, Zou et al[15] did not find statistically significant association of INSM1 with CgA and SYN (p-value < 0.09 and 0.494, respectively). In our study, sensitivity of INSM1, SYN, and CgA were 97, 96, and 86%, respectively. Comparison

Table 2 Correlation of INSM1 with clinicopathological variable

Variables	Total cases	Number of cases (%)		p-Value[a]
		INSM1 positive	INSM1 negative	
Histological types				
NET	29	28 (96.6)	1 (3.4)	00591
NEC	67	65 (97.0)	2 (3.0)	
Combined	4	4 (100)	0 (0)	
Site				
Lung	59	57 (96.6)	2 (3.4)	0.841
GIT and pancreas	31	30 (96.8)	1 (3.2)	
Others	10	10 (100)	0 (0)	
SYN				
Positive	96	94 (97.9)	2 (2.1)	0.008
Negative	4	3 (75)	1 (25)	
CgA				
Positive	86	83 (96.5)	3 (3.5)	0.011
Negative	14	14 (100)	0 (0)	

Abbreviations: CgA, chromogranin A; GIT, gastrointestinal tract; INSM1, insulinoma-associated protein 1; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; SYN, synaptophysin.
[a]Chi-square test.

Table 3 H-score comparison of SYN, CgA, and INSM1 by location of tumor

Tumor type	Antibodies	Positive cases	H-score (mean)
GIT	SYN	21/21	135
	CHR	18/21	128
	INSM1	21/21	188
Pancreaticobiliary system	SYN	9/10	144
	CHR	10/10	167
	INSM1	10/10	206
Lung NET	SYN	3/3	58
	CHRO	3/3	85
	INSM1	3/3	170
Lung SMCC	SYN	48/51	103
	CHR	43/51	80
	INSM1	49/51	194
Lung LCNEC	SYN	1/1	80
	CHR	0/1	0
	INSM1	1/1	270
Nasal cavity	SYN	1/1	90
	CHR	0/1	0
	INSM1	1/1	90
BOT	SYN	1/1	80
	CHR	1/1	120
	INSM1	1/1	190
Presternal	SYN	1/1	185
	CHR	1/1	250
	INSM1	1/1	160
UB	SYN	1/1	200
	CHR	1/1	190
	INSM1	1/1	260
Cervix	SYN	5/5	163
	CHR	4/5	74
	INSM1	5/5	198
Vault	SYN	1/1	285
	CHR	1/1	175
	INSM1	1/1	300

Abbreviations: BOT, base of tongue; CgA, chromogranin A; GIT, gastrointestinal tract; INSM1, insulinoma-associated protein 1; LCNEC, large cell neuroendocrine carcinoma; NET, neuroendocrine tumor; SMCC, small cell carcinoma; SYN, synaptophysin; UB, urinary bladder.

of sensitivity of INSM1 and conventional marker of previous study is discussed in ►**Table 5**.

In our study, we evaluated INSM1 and other conventional NE markers by calculating H-scores. The mean H-scores of INSM1, SYN, and CgA in our study were 194.5, 119.6, and 108.7, respectively. This is slightly lower than the study by Fujino et al.[16] In their study, the mean H-scores were 211, 191, and 122, respectively. However, in our study comparison of INSM1 H-score with traditional NE markers was statistically significant. This result was concordant with the study of Fujino et al[16] (p-value < 0.0001).

Conclusion

INSM1 is a superior immunohistochemical marker when compared with traditional NE markers (SYN and CgA). Statistically significant association was found between expression of INSM1 and SYN and CgA. However, larger prospective

Table 4 H-score comparison

Parameters	Number	*p*-Value[a]
SYN vs. INSM1		
SYN < INSM1	79	0.001
SYN > INSM1	18	
SYN = INSM1	3	
CgA vs. INSM1		
CgA < INSM1	76	0.001
CgA > INSM1	21	
SYN = INSM1	3	
SYN vs. CgA		
SYN < CgA	53	0.195
SYN > CgA	46	
SYN = CgA	1	

Abbreviations: CgA, chromogranin A; INSM1, insulinoma-associated protein 1; SYN, synaptophysin.
[a]Wilcoxon rank test.

Table 5 Comparison of expression of NE markers with previous study

Studies	INSM1 (%)	SYN (%)	CgA (%)
Our study	97/100 (97)	96/100 (96)	86/100 (86)
Fujino et al[16]	100/102 (98)	88/102 (86.2)	84/102 (82.3)
Rosenbaum et al[8]	27/30 (90)	29/30 (96.7)	21/30 (70)
Aldera et al[17]	59/69 (85.5)	63/69 (91.3)	48/69 (69.5)
McHugh et al[13]	89/110 (82.9)	109/110 (99.1)	96/110 (87.3)
Mukhopadhyay et al[6]	144/152 (95)	147/150 (98)	125/149 (84)
Kriegsmann et al[18]	276/372 (74.2)	319/372 (85.8)	289/372 (77.7)
Rooper et al[14]	99/103 (96.1)	79/103 (76.7)	67/103 (65.0)
Sakakibara et al[19]	120/141 (85.1)	87/141 (61.7)	74/141 (52.5)
González et al[20]	32/32 (100)	32/32 (100)	31/32 (97)

Abbreviations: CgA, chromogranin A; INSM1, insulinoma-associated protein 1; NE, neuroendocrine; SYN, synaptophysin.

studies should be undertaken to assess the site-based INSM1 expression as well as to investigate the role of INSM1 in prognosis of NEN.

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Conflict of Interest
None declared.

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Interferons as Neoadjuvant Chemotherapy for Giant Cell Tumor: A Hospital-Based Prospective Pilot Study

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Abstract

Introduction Neoadjuvant chemotherapy is now considered an effective way to treat Campanacci grade 2 and 3 giant cell tumors (GCTs). Assessment of these drugs is essential clinically, radiologically, and pathologically. This study analyzes the early results of angiogenesis inhibitors (interferons) in the aggressive GCT of bone.

Methodology A prospective pilot study was conducted from January 2021 to July 2022 including eight biopsy-proven GCT patients subjected to interferon therapy. Radiological assessment was done with changes on plain radiograph, computerized tomography scan, and magnetic resonance imaging. Histopathological examination was done by changes in the biopsy and resected segment.

Results Out of the eight patients included in the study, 26% ($n = 3$) were males and 62% ($n = 5$) were females, with mean age of the patients being 24.6 ± 8.48 years (range: 22–38). There was significant reduction of the size of swelling (p-value: 0.049), significant reduction in Visual Analog Scale score (p-value: 0.011), significant decrease in swelling size on radiograph (p-value: 0.012), significant marginal sclerosis (p-value: 0.001), significant neocortex formation on radiographs (p-value: 0.001), significant result in and osteoid formation (p-value: 0.001) on histology. Whereas Campanacci grade on plain radiographs, number of viable cells, and number of viable stromal cell were not statistically different in comparison with pretherapy and posttherapy status.

Conclusion Interferon therapy in a GCT has potential beneficiary effect in terms of clinical, radiological, and pathological outcomes. It might prove to be an effective alternative to standard neoadjuvant chemotherapy in the management of aggressive GCT of bones.

Level of Evidence III.

Keywords
- giant cell tumor
- neoadjuvant chemotherapy
- interferon
- Campanacci grading
- ICDS criteria
- RECIST criteria

Introduction

Giant cell tumor (GCT) is a peculiar benign neoplasm with features of local as well as distant aggressiveness. The bones around the knee are common sites, followed by the distal radius.[1] Owing to the variation in histology, clinical, and radiographic appearance, neoadjuvant chemotherapy has been used prior to different surgical options including local curettage, extended curettage to excision, and reconstructive arthroplasty.[2]

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Neoadjuvant chemotherapy, which has been used for the treatment of GCTs, are bisphosphonates (zoledronic acid), denosumab, and calcitonin.[3] Interferons were initially used for viral infection and acted by inhibiting protein synthesis. They have also been shown to act on the cells that exhibit basic fibroblast growth factor (BFGF). The cells of GCT also overexpress BFGF on them and so, in turn, will respond to interferon therapy by inhibiting angiogenesis. There have been reports of trying this drug in the GCT of the jaws and recurrent GCT with varying results, but very few studies are available for its use in musculoskeletal GCT.[4] This drug's limitation includes its increased administration frequency and prolonged use. It has also been shown to have allergic manifestation and flaring of autoimmune disorders.[5]

In view of the high recurrence rate in GCTs (0–65% depending on the type of treatment),[6] neoadjuvant chemotherapy is now considered an effective way to treat Campanacci grade 2 and 3 GCTs.[7] Quantification of response is important for the assessment of these drugs on the clinical and pathological effects of tumors.[8] These assessment tools not only help in evaluation but also guide for change in any treatment strategy. In combination with other indicators of patient condition, response evaluation helps in the therapeutic efficacy decision-making process.[9]

Clinical examination still holds good for the qualitative evaluation of the response of drugs to tumors. It not only gives the actual comparative assessment between the pre- and posttherapy but also gives an edge to the treating physician to decide the further mode in case of any untoward outcomes. Its disadvantage is that there are chances of bias and it is difficult to quantify.[9,10]

Imaging plays a pivotal role in the evaluation of the response of neoadjuvant chemotherapy in musculoskeletal disorders. The assessment of treatment response and residual tumor influence the patient's prognosis and surgical strategy.[11] The radiographic response has been correlated with improved local control and overall survival.[12]

Quantification of this radiological information in advanced imaging modalities like computed tomography (CT) scan and magnetic resonance imaging (MRI) identifies the early benefits of neoadjuvant chemotherapy and helps in limb salvage resections.[13] Since both clinical and radiological assessment is done before the biopsy and after the completion of neoadjuvant chemotherapy, comparative analysis can be easily done to establish the response to the drug treatment.[14]

In the available literatures, interferon has been used as an effective method for the treatment in recurrent GCT of the mandible and recurrent and metastatic GCT of the spine.[15,16] Its use in GCT has proven to play an effective role in various nonappendicular skeleton. However, there are lacunae in knowledge regarding the use of interferon as a neoadjuvant chemotherapy. This research aims to analyze the changes in the tumor in terms of clinical, radiological, and histological parameters to establish the drug treatment response after the use of interferons in musculoskeletal GCTs.

Methodology

A single center-based prospective cohort pilot study was conducted from January 2021 to July 2022 after obtaining clearance from the institutional ethical committee. Verbal and written consent was taken from all patients included in the study.

The histologically proven case of GCT of any bone between the ages of 20 and 40 years with Campanacci grade 2 and 3 GCT, including locally aggressive and recurrent GCT, subjected to interferon therapy, were included in the study. All patients with Campanacci grade 1 GCT, not ready to undergo systemic therapy or not fit for systemic therapy due to any systemic and autoimmune cause, and patients subjected to other systemic therapy like denosumab were excluded from the study.

After a biopsy-proven histopathological diagnosis of GCT, patients were subjected to routine biochemical investigations in the form of renal function test, liver function test, and thyroid function test, in addition to hemogram and dental examination. After ruling out possible autoimmune disorders, these patients were given interferons on alternate days. A total of 45 doses of interferons alfa-2b in a dose of 3 miu/m^2 of body surface area via a subcutaneous route on alternate days were given for a total 3 months' course, all patients received a full course of therapy of 45 cycles over 90 days on an alternate day basis.

The patient demographic data, site and side of the lesion and the duration of symptoms was assessed at the time of biopsy. Clinical, radiological, and histological assessment was done at the time of biopsy, followed by evaluation by the same parameters after the completion of interferons alfa-2b. Clinical assessment was done by the size of swelling, consistency of swelling as soft, firm, and hard, and pain score in the form of a Visual Analog Scale (VAS) from 0 to 10.[17] Radiological assessment was done with a plain radiograph, CT scan, and MRI. In the plain anteroposterior radiograph, the size of the lesion, the border of the lesion (Campanacci grading),[10] marginal sclerosis as an increase in opacity on a margin of radiolucent lesion, and neocortex formation were assessed (►**Supplementary Fig. S1**, available in the online version only). CT scan and MRI were performed where the longest diameter in the axial view in the CT scan and MRI was used in the pretherapy and posttherapy period, and the reduction in % of the size and increase in % of density was assessed (►**Figs. 1** ►**Fig. 2**).

% reduction in size (%S): The % reduction in size (%S) was calculated as:

$$\%S = \text{longest diameter pretherapy} - \text{longest diameter posttherapy} \times 100.$$[18]

Longest diameter pretherapy: The % increase in the density (%D) was assessed as:

$$\%D = (\text{pretherapy density}) - (\text{posttherapy density}) \times 100.$$[19]

Pretherapy Density

Size and density were calculated with the help of Radiant DICOM software. On the Radiant DICOM in the axial view of

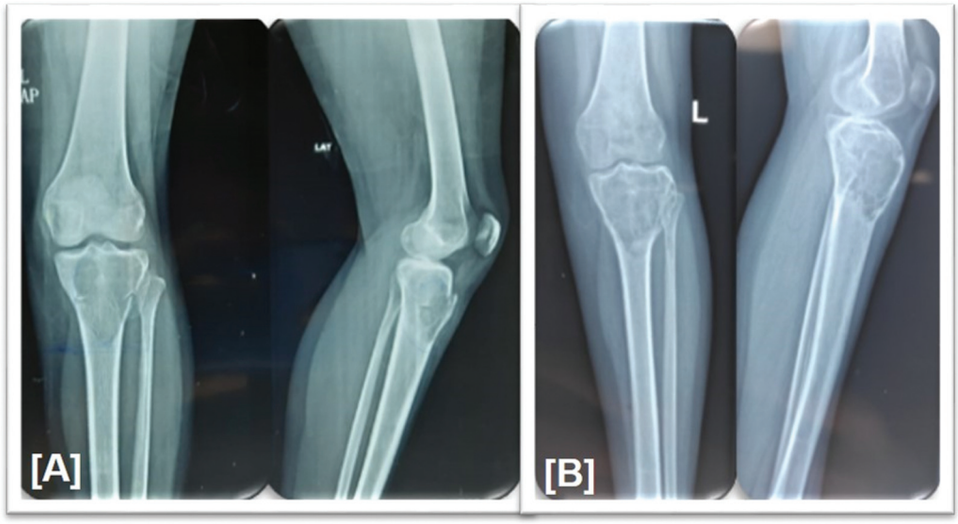

Fig. 1 Representative image of plain radiograph of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, for the assessment of the size of the lesion, the border of the lesion (Campanacci grading), marginal sclerosis, and neocortex formation.

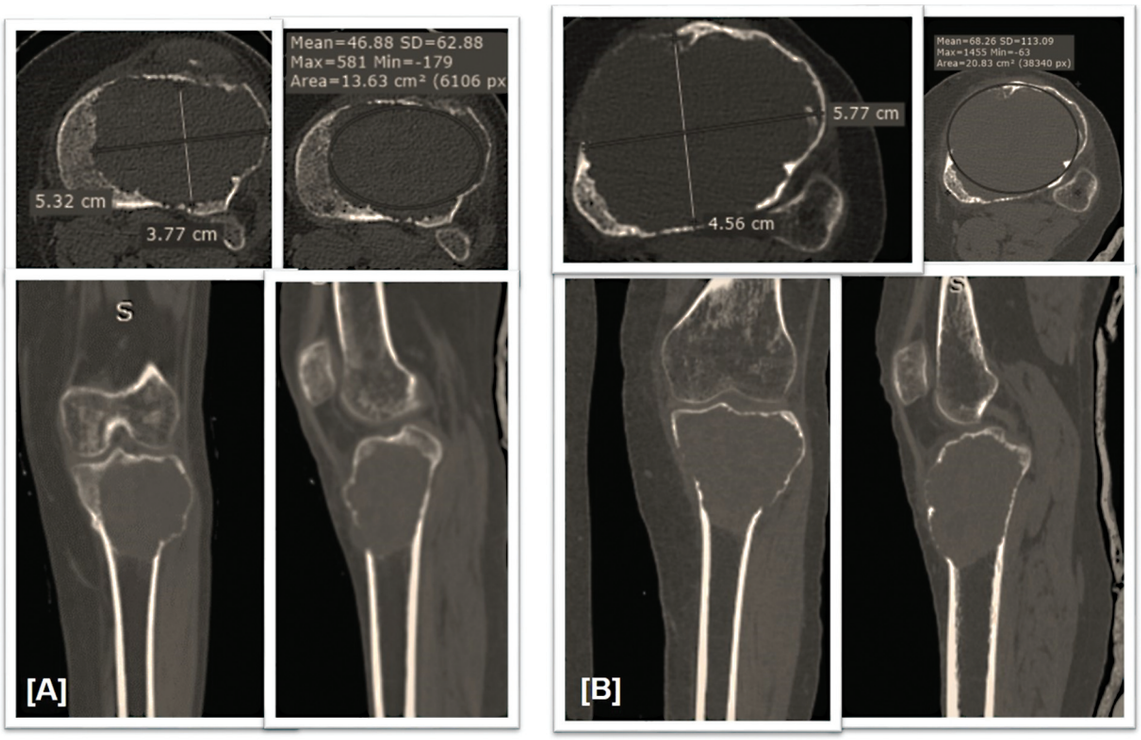

Fig. 2 Representative image of computed tomography (CT) scan of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, where the longest diameter in the axial view used to compare the reduction in % of the size and increase in % of density.

the involved segment, an ellipse was measured, and the mean density of the tumor was measured and calculated. The assessment criterion used was: inverse Choi density/size criteria (ICDS)[20] and Response Evaluation Criteria in Solid Tumor (RECIST).[21]

Histopathological assessment was done in the specimen of biopsy (pretherapy) and in the final histopathology obtained after curettage/resection in terms of the number of viable tumor cells, number of viable stromal cells, and osteoid formation (►**Fig. 3**).[22]

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York, United States). Results on continuous measurement is presented as mean ± standard deviation; median (interquartile range) and categorical as frequency and percentage. Paired *t*-test used to compare between the mean of the paired

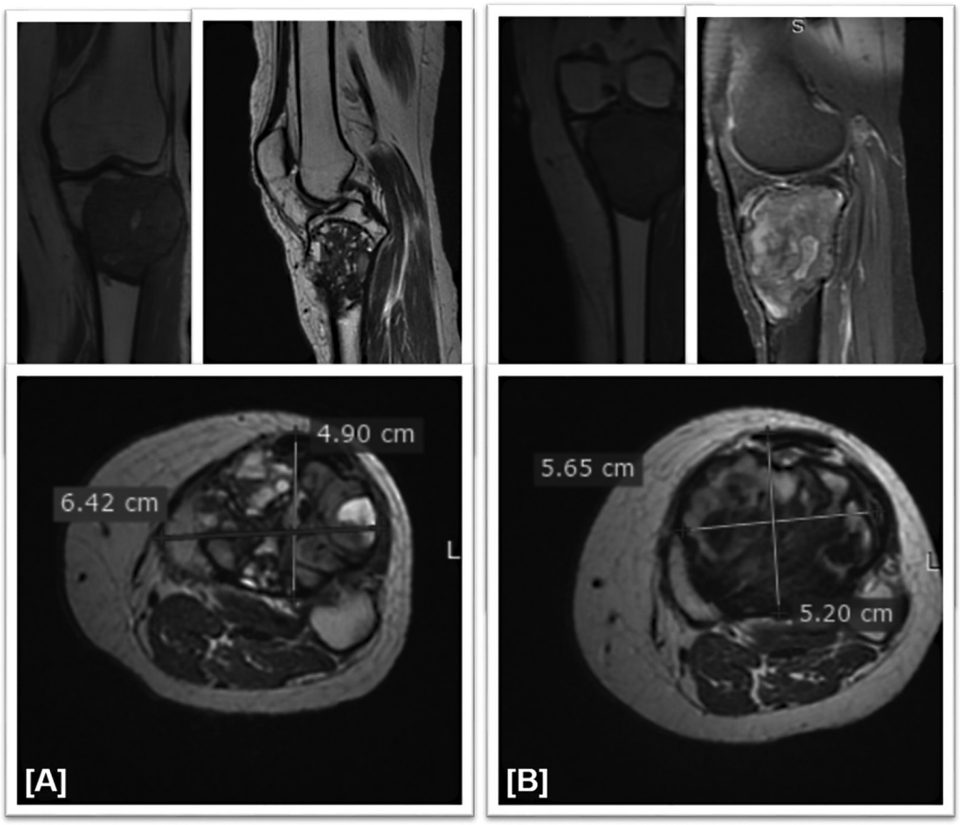

Fig. 3 Representative image magnetic resonance imaging (MRI) of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, where the longest diameter in the axial view used to compare the reduction in % of the size and increase in % of density.

samples.Inferential statistics like the Wilcoxon signed rank test (to compare median values pre- and posttherapy) and the McNemar test (compare count pre- and posttherapy) were used. A p-value of < 0.05 was considered statistically significant.

Result

Out of a total of 37 patients with proven histological GCT who attended to the tumor clinic of the department during the study period, five were between the ages of < 20 and > 40 years. Four patients were of Campanacci grade 1, two patients were not willing to systemic therapy, and one patient was fit for systemic therapy due to antinuclear antibody positive autoimmune disease, systemic lupus erythematosus. Out of 25 patients of Campanacci grade 2 and 3 fit for systemic therapy, patients were offered either denosumab or interferon according to the duration of systemic therapy required, compliance to more prolonged doses of therapy, and its cost-effectiveness. Among those included, 17 patients were willing to go for denosumab, and were excluded, and the final eight patients willing to go for interferon therapy were included in the study (►**Supplementary Fig. S2**, available in the online version only).

Patient's Demography

Out of the eight patients included in the study, 26% ($n = 3$) were males and 62% ($n = 5$) were females. The mean age of the patients was 24.6 ± 8.48 years (range: 22–38), with a median age of 21 years. Among the included cases, 37.5% ($n = 3$) were GCT of proximal tibia, 25% ($n = 2$) were GCT of distal end femur, 25% ($n = 2$) were GCT of distal end radius, and 12.5% ($n = 1$) were GCT of proximal humerus. The mean duration of symptoms of swelling was 6.12 ± 4.24 months (range: 2–12), with median duration of symptoms being 6 months (►**Supplementary Table S1**, available in the online version only). All the patients completed the treatment course and follow-up evaluation after completion of the course. Initial therapy manifested flu-like symptoms, myalgia, and fever after the first dose within 12 to 48 hours in three cases, which were managed by symptomatic nonsteroidal anti-inflammatory drugs, but on subsequent doses, there were no such side effects.

Clinical Assessment

The mean size of swelling prior to therapy was $27.20 \pm 10.57\,cm^2$ (18.0–42.0), and it was decreased to $22.62 \pm 8.66\,cm^2$ (15.0–36.0 after therapy) with a p-value of 0.049, which suggests there is a statistically significant reduction of the size of swelling observed pre- and posttherapy (►**Table 1**). The mean pretherapy VAS score for pain was 7.50 ± 0.54 (7.0–8.0) with median value of 7.50 (7.0–8.0), which decreased to mean VAS score of 2.88 ± 0.84 (2.0–4.0) with median value of 3.0 (2.0–3.5) after therapy with a p-value of 0.011, which suggests there is a statistically significant decrease in VAS score observed

Table 1 Comparison of clinical and radiological assessment pre- and posttherapy

Assessment	Status	*N*	Range	Median (IQR)	Mean ± SD	*p*-Value
Swelling	Pretherapy	8	18.0–42.0	20.5 (19.80–38.5)	27.20 ± 10.57	0.049[a]
	Posttherapy	8	15.0–36.0	20 (15–30)	22.62 ± 8.66	
VAS	Pretherapy	8	7.0–8.0	7.50 (7.0–8.0)	7.50 ± 0.54	0.011[a]
	Posttherapy	8	2.0–4.0	3.0 (2.0–3.5)	2.88 ± 0.84	
X-ray size	Pretherapy	8	10.50–48.0	22.14 (17.22–25)	24.17 ± 12.84	0.012[a]
	Posttherapy	8	9.81–48.28	11.95 (11.90–19.76)	18.94 ± 14.77	

Abbreviations: IQR, interquartile range; SD, standard deviation; VAS, Visual Analog Scale.
[a]Significant ($p < 0.05$).

pre- and posttherapy (►**Table 1**). All patients had firm consistency prior to therapy, which later changed to the firm to hard consistency after the completion of therapy.

Radiological Assessment

The mean size of tumor pretherapy was $24.17 \pm 12.84\,cm^2$ (10.50–48.0), which was decreased to $18.94 \pm 14.77\,cm^2$ (9.81–48.28) after therapy, with a *p*-value of 0.012, signifying a statistically significant decrease in swelling size pre- and posttherapy (►**Table 1**). Campanacci grading border of the lesion was grade 3 pretherapy in all cases, which remains constant in grade 3 after therapy in all cases with a *p*-value of 1.00, signifying improvement in Campanacci grade by the therapy. There was no marginal sclerosis and neocortex formation in all (100%, $n = 8$) cases prior to the therapy, but after the completion of therapy, there was marginal sclerosis and neocortex formation in all (100%, $n = 8$) cases, with a *p*-value of 0.001 in each, signifying there was a statistically significant marginal sclerosis and neocortex formation after the completion of therapy (►**Table 2**). The ICDS and RECIST score were taken posttherapy on CT scan and MRI. ICDS scoring according to the CT scan was partial response in 25% ($n = 2$), progressive in 25% ($n = 2$), and stable disease in 50% ($n = 4$). Whereas in MRI, the ICDS score was partial response in 37.5% ($n = 3$), progressive in 25% ($n = 2$), and stable disease in 37.5% ($n = 3$) (►**Table 3**). The RECIST score on CT scan was partial response in 12.5% ($n = 1$), progressive in 25% ($n = 2$), and stable disease in 67.5% ($n = 5$). Whereas in MRI, the RECIST score was partial response in 37.5% ($n = 3$), progressive in 25% ($n = 2$), and stable disease in 37.5% ($n = 3$) (►**Table 3**).

Pathological Assessment

The number of viable cells in pretherapy was 100%, which remained the same at 100% in posttherapy, with a *p*-value of 1.00, signifying no statistically significant result in the number of viable cells on histology by the therapy. The density of stromal cells before therapy was 3+ in 100% ($n = 8$) of cases, which changed to 2+ in 50% ($n = 4$) of cases and remained constant at 3+ in 50% ($n = 4$) of cases, with a *p*-value of 0.368, signifying no statistically significant result in the number of viable stromal cell on histology by the therapy. There was no osteoid formation in any of the cases pretherapy, whereas there was 5% osteoid formation in 37.5% ($n = 3$) cases and 10% osteoid formation in 67.5% ($n = 5$) cases, with a *p*-value of 0.001, showing statistically significant result in osteoid formation on histology after therapy.

Discussion

One of the most common primary musculoskeletal tumors is GCT of the bone.[1] In South India, the incidence was 30.3%, while in western India, the incidence was 6.3%.[23,24] The incidence of GCTs among patients between 20 and 40 years of age is higher.[25] A majority of these tumors occur in the epiphysis of bones around the knee, with a 66% incidence rate, followed by distal radius and proximal humerus.[25] In our study, we took cases between 20 and 40 years as GCT is most prevalent in this age. Our studies show almost similar results to the previous studies as the most common site affected by GCT in our study is around the knee, with 67.5% incidence, followed by the distal end radius (25%) and proximal humerus (12.5%).

Table 2 Comparison of radiological assessment pre- and postchemotherapy

		Yes *N* (%)	No *N* (%)	*p*-Value
X-ray Marginal sclerosis	Pretherapy	0	8 (100)	0.001[a]
	Posttherapy	8 (100)	0	
X-ray Neocortex formation	Pretherapy	0	8 (100)	0.001[a]
	Posttherapy	8 (100)	0	

[a]Significant ($p < 0.05$).

Table 3 Comparison of radiological assessment on CT scan and MRI in terms of ICDS and RECIST

CT ICDS versus MRI ICDS						
	Responses	MRI ICDS				Total
		Partial response	Progressive	Stable disease	Unable to evaluate	
CT ICDS	Partial response	1	0	1	0	2
	Progressive	0	2	0	0	2
	Stable disease	2	0	2	0	4
	Unable to evaluate	0	0	0	0	0
	Total	3	2	3	0	8
CT RECIST versus MRI RECIST						
	Responses	MRI RECIST				Total
		Partial response	Progressive	Stable disease	Unable to evaluate	
CT RECIST	Partial response	0	0	1	0	1
	Progressive	0	2	0	0	2
	Stable disease	0	0	5	0	5
	Unable to evaluate	0	0	0	0	0
	Total	0	2	6	0	8

Abbreviations: CT, computed tomography; ICDS, inverse Choi density/size criteria; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumor.

In most cases, surgery is the most effective treatment, especially for indolent, bone-confined tumors. A curettage procedure has been combined with adjuvant chemotherapy or radiation for biologically aggressive tumors or recurrent tumors.[26] Moderate-dose radiation therapy has been the typical treatment for patients with nonresectable GCT.[27] It has been reported that chemotherapy may provide palliative treatment for primary or secondary malignancies in GCT despite having marginal benefits in advanced stages.[28] In previous literature, it was found that denosumab reduced pain and improved functional status in nearly 90% of patients with recurrent or unresectable GCTs of the bone (either by eliminating giant cells or not progressing on radiographs).[29] For patients with metastatic GCT or advanced GCT who cannot undergo surgery, denosumab may be a viable treatment option.[29] In our study, we subjected the patients to neoadjuvant chemotherapy interferon just after the diagnosis of GCT on the patient's preference; it was found to decrease the size of the swelling and the tumor significantly. The patient's pain status in terms of VAS score was also significantly improved after the completion of interferon therapy. There is a significant improvement in radiographs on the development of marginal sclerosis and neocortex formation, which helps in the regression of the tumor and improvement in tumor progression. On interferon therapy, most of the tumor lesions stay at the stable lesion on radiographic ICDS and RECIST criteria.

Natural interferon alfa produced by leukocytes is both an antitumor and antiangiogenic protein.[30] By enhancing antigen expression, antiproliferative activity, and cytostatic activity, antitumor effects can be directly observed on cells, while indirect mechanisms include the cytocidal activity of macrophages, lymphocytes, and natural killer cells, cytokine production, and antibody modulation.[31] In addition to downregulating BFGF gene expression, interferon alfa and beta also inhibit tumor cell protein production.[5]

Kaban et al reported in 1999 using it to treat recurrent GCTs of the mandible.[15] Interferon therapy combined with curettage was a promising treatment strategy for aggressive GCTs. The combined treatment resulted in a higher tumor control rate with lower operative morbidity than conventional approaches.[26] Wei et al concluded that interferon alfa-2b might be an effective and safe treatment for spine GCT recurrence and metastasis in soft tissue after studying interferon alfa-2b for recurrent and metastatic GCT of the spine.[16] In a similar fashion, Goldman et al, Schütz et al, O'Connell and Kearns, and Tarsitano et al studied interferon alfa-2A after mandible surgery and found complete tumor remission.[32–35]

In the available literature, fever and flu-like symptoms were documented during the first 24 to 48 hours of the treatment, which disappeared spontaneously without treatment. Also, there is evidence of the development of leukocytopenia and thrombocytopenia, which might need to stop the therapy temporarily.[16] Similarly, in our study, 37.5% ($n = 3$) manifested flu-like symptoms, myalgia, and fever after the first dose within 12 to 48 hours, which were managed by symptomatic nonsteroidal anti-inflammatory drugs, but on subsequent doses, there were no such side effects. Compliance is another problem that needs to be dealt with for the longer duration of injectable dose, which may result in poor compliance. In our case, drugs were administered either under direct supervision or with proper instruction at a nearby primary health center with proper documentation of the drug chart to maintain good compliance, hence all patients completed the full course of therapy.

A thorough search of the literature revealed that the experience has been limited to patients with metastatic disease or locally aggressive, unresectable GCTs or those refractory to radiation therapy. To our knowledge, no previous studies were conducted to see early results of interferon in GCTs after the histological diagnosis. In our study, interferon demonstrated early clinical and radiological improvements after the completion of therapy by reducing tumor size and increase in stromal density. Histologically, it maintained a constant number of viable cells, stromal cells, and osteoid formation following therapy.

Conclusion

To conclude,

- Clinical, radiological, and histological evaluation of interferons has its potential role in the treatment of aggressive GCTs of the bone as neoadjuvant chemotherapy, which helps in tumor regression and progression with a reduction in tumor grading, which smoothens the surgical procedure and overall improvement in a functional outcome.
- With the use of interferon alfa-2b, there was a significant reduction of the size of swelling, a reduction in a VAS score, decrease in swelling size on radiograph, significant marginal sclerosis, significant neocortex formation on radiographs, and significant result in osteoid formation on histology. Whereas no significant improvement in Campanacci grade on plain radiographs, number of viable cells, and number of viable stromal cells were seen in comparison with pretherapy and posttherapy status.
- Taking the drug for a long duration on alternate days by parenteral route is the only disadvantage seen, which needs proper documentation and instruction for compliance.
- The limitation of this study includes small sample size due to less preference of patients in terms of prolonged doses and its compliance. Long-term effect of this drug on the recurrence of the tumor still needs to be evaluated. In addition, large studies are still required to know the potentiality of interferons in comparison to the standard neoadjuvant therapy.

Patient Consent

Consent was taken with each individual for the enrollment of study and publication of data on research paper. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical Review Committee Statement

Clearance obtained from institutional ethical clearance committee. A copy of the Certificate of Ethical Clearance is available for review by the Editor-in-Chief of this journal on request.

Authors' Contributions

S.P.S.: Planning of study, data management, writing, and revising the manuscript.
A.R.: Data management and manuscript preparation.
B.B.N.: Data management and manuscript preparation.
A.S.: Data management.
M.D.: Planning of study, revising the manuscript, and as corresponding author.

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Conflict of Interest

None declared.

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Trilaciclib: A Novel Approach to Mitigate Chemotherapy-Induced Myelosuppression in Cancer Treatment

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Abstract

Trilaciclib, a novel cyclin-dependent kinase 4/6 inhibitor, has demonstrated the ability to protect bone marrow from chemotherapy toxicity, improving patients' quality of life (QoL). This review describes the mechanism of action, efficacy, and toxicity profile of trilaciclib. Trilaciclib halts retinoblastoma protein phosphorylation during the early G1 phase, preventing the transition from the G1/S phase and inducing the cell cycle arrest in the G1 phase, which protects the hematopoietic cell lineages. Trilaciclib is indicated by the United States Food and Drug Administration and National Comprehensive Cancer Network to decrease the incidence of chemotherapy-induced myelosuppression in adult patients before a platinum/etoposide or topotecan containing regimen for extensive stage small cell lung cancer. Its ease of administration as an intravenous infusion, given before starting chemotherapy, and the favorable side effect profile make it a better-tolerated drug, improving patient QoL.

Keywords
- trilaciclib
- neutropenia
- CDK 4/6 inhibitor
- chemotherapy-induced myelosuppression

Introduction

Myelosuppressive chemotherapeutic agents have an associated risk of chemotherapy-induced myelosuppression (CIM). Neutropenic complications include febrile neutropenia, prolonged hospitalization days, and increased mortality rates.[1] Granulocyte colony-stimulating factor (G-CSF) reduces these side effects and improves patient outcomes.[2] However, financial burden, side effects of G-CSF, including bone pain, administration after chemotherapy mostly in a home-based setting, multiple uses of injections, and continued vulnerability to infection after chemotherapy remain unmet needs.[3–5] It is challenging to ensure the cold chain maintenance for the G-CSF injection and patient compliance in home-based settings, especially in the illiterate population. Trilaciclib, a novel cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, has shown promise in achieving this balance. Its ease of administration as an intravenous injection given just before chemotherapy addresses the logistic issues associated with traditional G-CSF injections.

This review delves into trilaciclib's mechanism of action, preclinical and clinical studies, safety profile, and potential applications. By preserving bone marrow and immune cells during chemotherapy, trilaciclib minimizes myelosuppression impact and promotes a more efficient approach to treatment.

Discovery, Mechanism of Action, Pharmacokinetics, Indications, and Contraindications

Trilaciclib's development stemmed from advancements in understanding the role of CDK4/6 in cell cycle regulation and the need for improved strategies to protect patients from chemotherapy's myelosuppressive effects. G1 therapeutics spearheaded the drug's research and conducted a series of

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Table 1 Data for Trilaciclib

Study	Phase	Disease	Intervention	FN	Hospitalization Rate
NCT03041311 (2020)	2	ES-SCLC	Trilaciclib (240 mg/m^2 OD DAY 1–3) before Carboplatin DAY 1 + Etoposide DAY 1-3 + Atezolizumab DAY 1 → Atezolizumab maintenance DAY 1 (CYCLE Q21D)	1.9%	3.8%
NCT02978716 (2019)	2	TNBC	Group 1: Gemcitabine + Carboplatin D1,8	3%	N/A
NCT02499770 (2019)	1b/ 2	ES-SCLC	Trilaciclib (200/240 mg/m^2 OD DAY 1–3) before Carboplatin DAY 1 + Etoposide DAY 1–3	3%	N/A
NCT02514447 (2021)	1b/2a	ES-SCLC	Trilaciclib (240 mg/m OD D1–3) prior to (≤4h) Topotecan D1-5d Q21D	6.3%	9.4%

Abbreviations: ES-SCLC, extensive stage small cell lung cancer; FN, febrile neutropenia; Q21D, every 21 days; OD, once daily; N/A, Not Available.

Table 2 Ongoing Clinical Trials

Study	Phase	Disease	Drugs	Status
PRESERVE 1 (NCT04607668)	3	m CRC	FOLFOXIRI / Bevacizumab + Trilaciclib V/s Placebo	Ended (placebo outperformed trilaciclib)
PRESERVE 2 (NCT04799249)	3	m TNBC	Gemcitabine / Carboplatin + Trilaciclib V/s Placebo	Active
PRESERVE 3 (NCT04887831)	2	Advanced / metastatic bladder cancer	Chemotherapy and/or Trilaciclib Followed By Avelumab	Active
PRESERVE4 (NCT04863248)	2	NSCLC	Docetaxel + Trilaciclib Vs Placebo	Terminated
NCT04902885	3	ES SCLC	Carboplatin / Etoposide Or Topotecan + Trilaciclib V/s Placebo	Recruitment completed

Abbreviations: ES SCLC, extensive stage small cell lung cancer; FOLFOXIRI, folinic acid, 5- fluorouracil, oxaliplatin and irinotecan; m CRC, metastatic colorectal cancer; m TNBC, metastatic triple negative breast cancer; NSCLC, non small cell lung cancer.

pivotal trials. This led to its emergence as a promising myelopreservation agent in cancer therapy.

Trilaciclib (G1T28) selectively inhibits CDK4/6, crucial cell cycle regulators. This action halts retinoblastoma protein phosphorylation during the early G1 phase, preventing transition from the G1/S phase and inducing cell cycle arrest in the G1 phase. This protects the hematopoietic cell lineages (red blood cells [RBCs], platelets, neutrophils, and lymphocytes) from the cytotoxic effects of chemotherapy. Additionally, trilaciclib triggers apoptosis and inhibits the proliferation of tumor cells overexpressing CDK4/6. Moreover, for patients with CDK4/6-independent tumor cells, the drug protects against CIM. This safeguarding mechanism reduces myelosuppression and heightens immune responses during cancer treatment.[6]

Trilaciclib has an average terminal half-life of approximately 14 hours, primarily eliminated through the fecal route, with a minor contribution via the renal route. No dose adjustments are required according to differences in age, sex, or hepatic or renal function.

Trilaciclib is indicated by the United States Food and Drug Administration to decrease the incidence of CIM in adult patients before a platinum/etoposide or topotecan-containing regimen for extensive stage small cell lung cancer (ES-SCLC). National Comprehensive Cancer Network recommends trilaciclib as an option for decreasing the incidence of CIM in ES-SCLC. It is contraindicated in patients with a history of severe hypersensitivity to the drug. Ongoing research aims to explore its application in various cancer types and treatment regimens. Additionally, investigations are underway to evaluate its use in hematopoietic stem cell transplantation and radiation therapy.

Pivotal Trials

The pre-existing data for Trilaciclib and the various ongoing trials are provided in ►**Table 1** and ►**Table 2**. Trilaciclib has been shown to have benefits beyond preventing neutropenia and protecting other hematopoietic lineages such as RBCs and platelets. Trilaciclib can reduce the incidence of grade 4 neutropenia, grade ¾ anemia, thrombocytopenia, RBC transfusions, and erythropoiesis-stimulating agent administration. Additionally, trilaciclib has been shown to improve the quality of life (QoL). However, it is essential to note that these benefits may be tumor or chemotherapy-specific.[7,8]

Dosage and Administration

The recommended dose of trilaciclib is 240 mg/m^2 per dose. It is administered as a 30-minute intravenous infusion. It should be given 4 hours before starting chemotherapy. At most, the interval between two consecutive day doses should be 28 hours.

Safety Profile

Trilaciclib has demonstrated a favorable safety profile in clinical trials. Common side effects reported were mild and transient, including fatigue (9.5%), nausea (7.8%), anemia (5.9%), and infusion-related reactions (5.9%). The low incidence of severe adverse events suggests its potential for broad clinical use.[9]

Conclusion

In conclusion, trilaciclib can safeguard bone marrow cell lineages during chemotherapy, minimizing myelosuppression and enhancing immune responses, thus holding promise in improving patient outcomes. Trilaciclib offers hope for better patient compliance and QoL with its ease of use and favorable safety profile. Trilaciclib's potential applications in other cancer types and its role in hematopoietic stem cell transplantation and radiation therapy can improve cancer care in the future.

Note

No prior submissions.

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

Patient Consent

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Conflict of Interest

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Anaplastic Thyroid Carcinoma versus Metastatic SCC: A Diagnostic Dilemma in a Rare Presentation of Post-Radiation Thyroid Swelling

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Abstract

A 71-year-old male with type 2 diabetes and hypertension was diagnosed with carcinoma of the pyriform fossa in 2019. The biopsy was reported as a moderately differentiated squamous cell carcinoma, and positron emission tomography-computed tomography (PET-CT) scan showed an fluorodeoxyglucose (FDG)-avid lesion in the pyriform fossa and the aryepiglottic fold with few nodes in level II and level III. The paitent was treated with radical chemoradiotherapy. A follow-up PET-CT scan done in 2022 revealed an FDG-avid soft tissue thickening in the left palatine tonsillar region and an uptake in the thyroid that was reported as not significant. A punch biopsy from the tonsillar fossa lesion revealed squamous cell carcinoma. The lesion was treated as a second primary and treated with radiotherapy with curative intent. The patient was complaining of dysphagia, difficulty in breathing, and weight loss around 6 months after treatment that were addressed medically. There was a significant reduction in size and FDG activity of the ill-defined thickening in the left tonsillar region which was seen in the response-assessment PET done 6 months after RT. A heterogeneously enhancing nodules were seen in both lobes of the thyroid in which the largest one measured 3.5×3.1 cm seen in the right lobe. The patient underwent a biopsy from the thyroid that revealed a benign thyroid gland infiltrated by clusters and nests of poorly differentiated malignant cells. The histomorphology was suggestive of a poorly differentiated carcinoma, likely anaplastic carcinoma thyroid, or metastasis of the squamous cell carcinoma. Curative treatment was ruled out in this case due to his comorbidities, pulmonary symptoms, and radiation delivered to the neck.

Keywords

- anaplastic thyroid carcinoma
- medical oncology
- metastatic squamous cell carcinoma
- nuclear medicine
- pathology
- radiation oncology

Case Report

A 71-year-old male with type 2 diabetes and hypertension was diagnosed with carcinoma of the pyriform fossa in 2019. The biopsy reported a moderately differentiated squamous cell carcinoma (SCC), and positron emission tomography-computed tomography (PET-CT) scan showed a lesion in the pyriform fossa and the aryepiglottic fold with few nodes in level II and level III. No other sites showed any pathological uptake. He received concurrent chemoradiotherapy in 2019 with 6 cycles of weekly cisplatin and 33 fractions of radiation. PET-CT scan done in 2021 showed complete response. A follow-up PET-CT scan done in 2022 revealed an fluorodeoxyglucose (FDG)-avid soft tissue thickening in the left palatine tonsillar region and an uptake in the thyroid that was reported as not significant. A punch biopsy from the tonsillar

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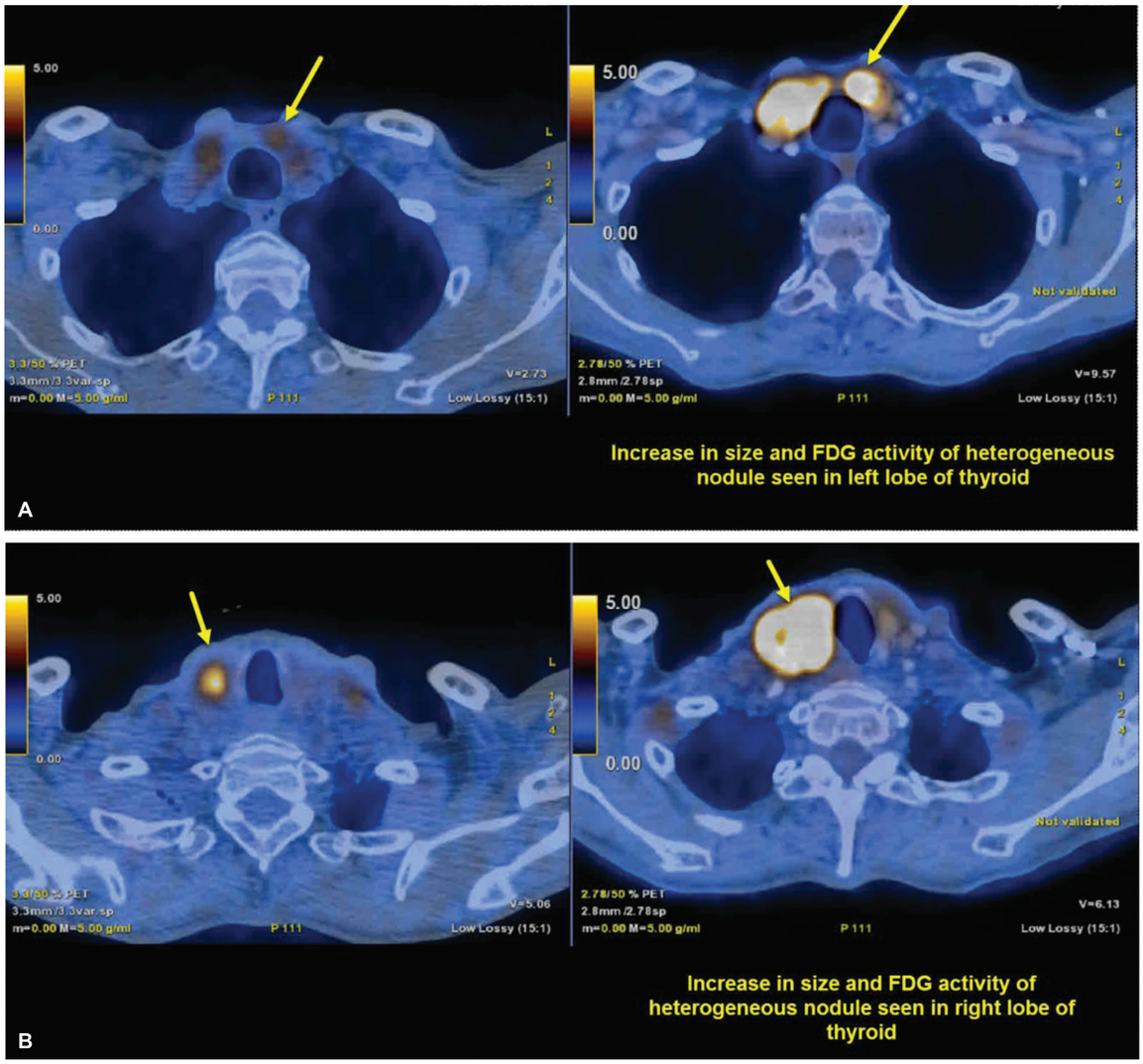

Fig. 1 FDG-avid (SUV max. 15.5) heterogeneously enhancing nodules were seen in both lobes of the thyroid.

fossa lesion revealed SCC. The case was discussed in a multidisciplinary tumor board at our institution. The lesion was concluded to be a second primary and was treated with curative radiotherapy only. He received 66 Gy in 30 fractions. A response assessment PET-CT scan was done 6 months after the completion of radiation. The patient complained of dyshphagia, dyspnea, and weight loss that were addressed medically. There was a significant reduction in the ill-defined thickening in the left tonsillar region. However, FDG-avid (standardized uptake value [SUV] max. 15.5) heterogeneously enhancing nodules were seen in both lobes of the thyroid, the largest being 3.5×3.1 cm in the right lobe. The lesion appears to abut the right common carotid artery with the loss of the intervening fat plane and appeared to cause mass effect on trachea. (►**Fig. 1A** and **B**).

The patient underwent a biopsy from the thyroid that revealed a benign thyroid gland infiltrated by clusters and nests of poorly differentiated malignant cells. The histomorphology suggested a poorly differentiated carcinoma, likely anaplastic carcinoma thyroid or metastasis of the SCC. Immunohistochemistry (IHC) was done and the tumor cells expressed P40 (diffuse). The cells were immunonegative for TTF1 and PAX8. PAX8 is positive in only half of the anaplastic thyroid carcinoma. PAX 8 negativity does not rule out primary thyroid carcinoma. However, considering the history of SCC, metastatic SCC is favored over primary anaplastic carcinoma.(►**Fig. 2A**—10X; ►**Fig. 2B**—20X).

Curative treatment was ruled out due to his comorbidities, pulmonary symptoms, and radiation received. The patient was subsequently taken up for tracheostomy followed by palliative care.

Discussion

Anaplastic carcinoma of the thyroid is a rare entity. It accounts for 2 to 3% of all thyroid neoplasms and is associated with a poor prognosis.[1] Most of the thyroid malignancies caused by radiation are papillary thyroid

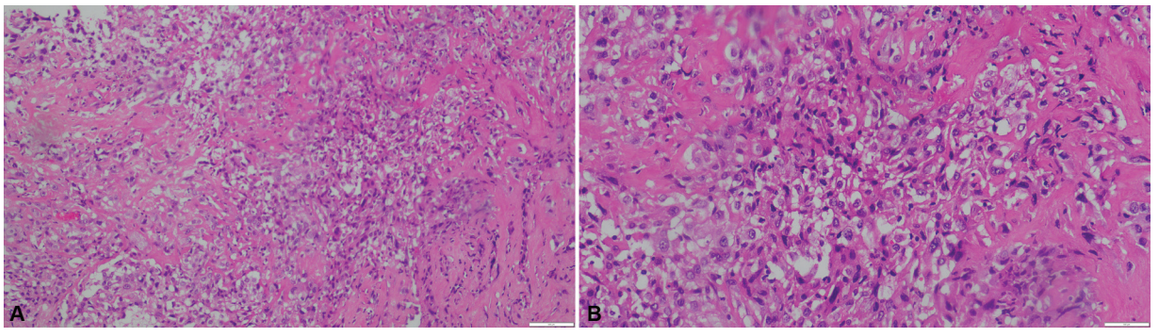

Fig. 2 The patient underwent a biopsy from the thyroid that revealed a benign thyroid gland infiltrated by clusters and nests of poorly differentiated malignant cells. Individual cells are ovoid with moderate clear cytoplasm and high N:C ratio. Areas of necrosis are seen.

cancers. ATC- Anaplastic Thyroid Cancer post head and neck irradiation has limited reporting in the past, mostly in postmortem cases.[2] A diagnostic dilemma, as was in the case of our patient, may occur as SCC with keratinization and/or intercellular bridges is a defining cytological feature of anaplastic thyroid carcinoma that is a characteristic feature of SCC as well. Squamous cells are found in 21% of all ATCs.[3] Cytokeratin and p53 are tumor markers in both ATC and squamous cell head and neck cancers.[3,4] Tumor-specific IHC markers such as PAX8 polyclonal, TTF-1, and thyroglobulin must be included routinely in doubtful cases where treatment in the curative setting is an option. The treatment for ATC and SCC in the recurrent/relapse setting is either surgery or radiotherapy.[5,6] Chemotherapy is seldom useful.

A significant number of ATC cases are reported to have programmed death-ligand 1 (PD-L1) immunopositivity. PD-L1 positivity can be found anywhere between 22 and 94% of the cases, depending on the detection techniques and cutoff levels employed.[7] However, a meta-analysis by Girolami et al was unable to show any association between ATC PD-L1 immunoexpression and survival.[8] BRAF V600E has been reported to have a high incidence in squamous cell cancers of the head and neck in India.[9] Dabrafenib and trametinib have been found to significantly improve the overall survival of anaplastic thyroid carcinoma patients, as well as in head and neck SCC.[10,11] Patients, though, can be offered the option of immunotherapy or targeted therapy when all other lines of management have failed or cannot be offered.

The thyroid uptake was reported as not significant which led to it not being investigated. Retrospectively, however, we believe that any suspicious nodule in the thyroid in patients receiving head and neck radiation must be investigated further. Patients who have received curative doses of radiotherapy must be monitored closely to rule out field cancerization as well as new primary malignant lesions. This would help make the intent of many such cases from palliative to curative if detected on time.

Palliative care includes airway management, nutrition optimization, and pain management, while alleviating other symptoms.[12]

Declaration of Patient Consent

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

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

Criteria for inclusion of authors—Case management, data collection, proofreading the content.

Data Sharing Statement

All data generated and analyzed during this study are included in this published article. Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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How I Treat Advanced Head Neck Cancer

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Introduction

In India, head and neck cancer including all sites is the most common cancer in terms of incidence and mortality among both sexes combined as per GLOBOCAN 2018, with lip and oral cavity being the most common site.[1] Squamous cell cancer of head neck (HNSCC) constitutes the majority of all head and neck malignancies.[2] Most of the patients present in the advanced stage.[3] Even localized HNSCC are notorious for high rates of recurrence in spite of curative modalities of treatment.[4] Treatment for advanced recurrent HNSCC is palliative systemic therapy provided that patients have a good Eastern Cooperative Oncology Group (ECOG) performance score (PS) with normal organ function.

Platinum-based systemic therapy is the standard of treatment in advanced metastatic HNSCC over a long period of time. Over time, antiepidermal growth factor receptor (EGFR) monoclonal antibody like cetuximab showed additional survival benefit over platinum-based therapy.[5] Recently, immune-checkpoint inhibitors (IOs) have been found to benefit both in first- and second-line settings as a single agent or in combination with platinum-based therapy.[6] Last but not the least, metronomic therapy has shown a survival benefit in recurrent metastatic settings.[7] In addition to systemic therapy, supportive care in controlling the symptoms is absolutely essential in the management of advanced HNSCC.[4]

India is a low middle-income country with a per capita income of Rs 11,254/- only. Majority of the people are not covered by health insurance.[8] The cost of modern therapies like cetuximab and IOs are beyond the reach of most people from India. Hence, the treatment of any cancer including metastatic HNSCC has to be tailored based on the financial affordability of the patients and it should be used as an important factor to decide the systemic therapy.

Case 1

A 50-year-old male with a history of tobacco consumption presented with an ulcerated lesion over the lateral border of the tongue for the last 4 months. On clinical examination, there was an ulcerated lesion measuring 4 × 4 cm with matted cervical lymphadenopathy. Biopsy of the lesion revealed a squamous cell carcinoma. Staging work-up revealed multiple lung metastases. His ECOG PS was 1 and his organ functions were within normal limits. The patient could not afford the targeted therapy and immune checkpoint inhibition as his monthly salary was Rs 15,000/- only. How to treat the patient?

The above patient was a case of de novo metastatic HNSCC. As the patient could not afford targeted therapies including immune checkpoint inhibitors, the patient could be treated with systemic therapy only. Historically, methotrexate alone was the standard systemic in recurrent metastatic HNSCC with a response rate of around 30%.[7] Phase II trials have shown that cisplatin alone had a similar response rate to single-agent methotrexate with increased toxicity.[9] Carboplatin is a platinum analog with a better toxicity profile in contrast to cisplatin. Carboplatin has also shown a response rate of around 24% in the metastatic HNSCC with greater ease in administering the drug.[10]

Based on the encouraging response rates, a trial was made to use combination therapy in this setting. Phase III Southwest Oncology Group study was planned to see the effect of combination chemotherapy over single-agent methotrexate with the primary objective being to see response rate of doublet therapy over a single agent. It was a three-armed study. The study arms were a combination of cisplatin and 5 fluorouracil (5FU) and carboplatin and 5 FU with single-agent methotrexate being the control arm. The overall response rates were 32, 21, and 10%, respectively, with the difference in response rate between cisplatin and 5FU being

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statistically significant than single-agent methotrexate.[11] Overall survival (OS) among the three arms were similar.

There was increased grade 3 and higher hematological toxicity along with renal toxicity in the cisplatin and 5FU arm. Based on this study, cisplatin and 5FU became the standard of therapy in metastatic HNSCC.

There was increased toxicity in the cisplatin and 5FU arm and it was attributed to the usage of 5FU. An attempt was made to replace 5FU with paclitaxel. Phase III trial (E1395) was planned to compare cisplatin and 5FU with a combination of cisplatin and paclitaxel.[12] The response rate and OS in both the arms were comparable with less gastrointestinal and hematological toxicity in the paclitaxel arm.

Docetaxel was also used in combination with cisplatin in many phase II studies and they have shown response rates varying between 30 and 50%.[13,14] No phase III trial has been conducted with this combination.

Pemetrexed—an antifolate analog—has been also tried in combination with cisplatin in advanced HNSCC. Phase III study was done to compare the efficacy of cisplatin pemetrexed over cisplatin alone. There was no added survival benefit with the doublet regime over single agent. But in post planned subset analysis, it was found that there was survival benefit in patients with oropharyngeal primary and with ECOG PS 0–1.[15]

In summary, combination chemotherapy has shown only improved response rate over single-agent therapy at an added cost of increased toxicity. None of the studies have shown OS benefit with combination therapy.[10,16]

Case 2

A 45-year-old female with a history of tobacco consumption presented with an ulcerated lesion over the buccal mucosa for the last 4 months. On clinical examination, there was an ulcerated lesion measuring 4 × 4 cm and with matted cervical lymphadenopathy. Biopsy of the lesion showed squamous cell carcinoma. Staging workup revealed multiple lung metastases. Her ECOG PS is 1 and her organ functions are within normal limits. Patient could afford targeted therapy. How to treat the patient?

Treatment benefit with systemic chemotherapy alone is modest in metastatic HNSCC. Targeted therapies including monoclonal antibodies and very recently immunotherapies have shown improved survival benefit when compared with systemic therapy alone.

Tumor cells from HNSCC do express high levels of EGFR and it is associated with poor prognosis.[17,18] Cetuximab is a chimeric monoclonal antibody that binds to EGFR receptor and causes cell death through antibody dependent cytotoxicity. It has been found to have a synergistic effect in combination with chemotherapeutic agents.[19,20]

In the landmark phase III EXTREME trial, cetuximab was used in combination with cisplatin 5FU and it was compared with the chemotherapy arm.[5] It was found that there is an absolute OS advantage of 2.8 months (hazard ratio [HR]: 0.8; 95% confidence interval [CI]: 0.64–0.99; $p = 0.04$) in the cetuximab arm. There was a higher incidence of hypomagnesemia, skin rash, infusion reaction, and sepsis related to cetuximab.

In view of concerns regarding toxicity with cisplatin 5FU, cetuximab has been used with taxane and cisplatin. In the TPExtreme trial, cetuximab was used with either cisplatin 5FU or cisplatin docetaxel.[21] There was a similar OS in both the arms with less toxicity and reduced rates of discontinuation in the taxane combination group, thus making another alternative regime for metastatic HNSCC.

Panitumumab is a fully humanized monoclonal antibody against EGFR receptor. It has a similar mechanism of activity with cetuximab and has shown comparable results to cetuximab in metastatic colon cancer.[22] It was expected that panitumumab will also show positive results in patients with metastatic HNSCC. But a phase III SPECTRUM trial that compared cisplatin 5FU with or without panitumumab failed to show an OS advantage in the arm containing panitumumab.[23] Additionally, the panitumumab-based regime had a higher incidence of toxicity also. Only in unplanned subgroup analysis, the benefit of panitumumab was there in p16 negative and oral cavity tumors.

Case 3

A 56-year-old female with a history of tobacco consumption presented with an ulcerated lesion over the buccal mucosa for the last 4 months. On clinical examination, there was an ulcerated lesion measuring 4 × 4 cm and with matted cervical lymphadenopathy. Biopsy of the lesion revealed squamous cell carcinoma with a combined positive score (CPS) score of 18%. Staging workup revealed multiple lung metastases. Her ECOG PS was 1 and her organ functions were within normal limits. How to treat the patient?

IOs have been tried in metastatic HNSCC. For usage of IO in renal cancers and melanoma, no biomarker is required; while for usage in thoracic malignancies, program death ligand (PDL1) staining score is used as an indicator to use IO either as a single agent or in combination with chemotherapy.[24] PDL1 staining is done on the tumor cells to calculate tumor proportion score (TPS) and various platforms have been used for the same. In HNSCC, instead of TPS scoring a CPS is calculated. In CPS scoring system, intensity is measured not only on the tumor cells but also on the lymphocytes and macrophages. CPS has been found to be a better predictor for response to IO.[25]

Pembrolizumab, a PD 1 inhibitor, has been approved to be used in the first line of metastatic HNSCC. It can be used either as a single agent or in combination with platinum-based therapy based on the phase III KEYNOTE 048 study.[26] In this trial, de novo recurrent metastatic HNSCC patients irrespective of PDL1 score were randomized to three arms. They were pembrolizumab monotherapy, pembrolizumab with platinum and 5FU, and cetuximab with platinum and 5FU and the primary endpoint of the trial being OS. It was found that there was an OS advantage with either pembrolizumab alone or pembrolizumab with chemotherapy over the cetuximab chemotherapy combination in patients with

CPS > 1. However, OS benefit with pembrolizumab and chemotherapy over cetuximab-based combined therapy was persistent in the whole population irrespective of PDL1 status, but with pembrolizumab monotherapy, the OS was non inferior only to cetuximab arm. The median duration of response was prolonged in both the IO arms. Contrary to the OS advantage, the progression-free survival (PFS) advantage was not there in either the pembrolizumab alone or the combined arm over the chemotherapy. The added OS advantage in spite of inferior PFS was postulated to the alteration of the tumor microenvironment with better sensitivity to subsequent therapy. But this postulation is controversial at present.

The distinction to choose IO alone over combination of IO with chemotherapy in patients with CPS > 1 is not very clear and it is arbitrarily based on the disease burden and symptom complex with pembrolizumab monotherapy is recommended for lesser disease burden with not much symptom complex.

Case 4

A 69-year-old male with a history of tobacco consumption presented with an ulcerated lesion over the gingival sulcus for last 4 months. On clinical examination, there was an ulceroproliferative lesion measuring 5 × 5 cm and with matted cervical lymphadenopathy. Biopsy of the lesion was squamous cell carcinoma. Staging workup revealed multiple lung metastases. His ECOG PS is 2 and he was a coolie with a monthly income of around Rs 1,000 and he could not afford a daycare-based therapy. How to treat the patient?

Treatment of metastatic HNSCC is diverse and it ranges from systemic chemotherapy to monoclonal antibody and recently IOs. The last two options are very expensive in the setting of low middle-income countries like India, leading to less penetration to the patient population. The standard systemic chemotherapy has only shown a modest benefit with associated toxicity. Recently, metronomic therapy has been found to be beneficial in metastatic HNSCC.

Principle of metronomic therapy is repeated administration of selected chemotherapeutic agents at a low dose, which in turn inhibits angiogenesis and also has additional immunomodulatory effects leading to tumor control.[27] Metronomic therapy has found to be beneficial in metastatic HNSCC also.[28] Various agents have been used, most commonly being methotrexate and celecoxib and most were in phase I to II studies. Oral capecitabine has also been used in some cases. Only recently, a phase III study was conducted where metronomic therapy was compared with single-agent cisplatin with the primary objective being OS benefit of metronomic therapy over chemotherapy.[7] Here, patients were randomized to receive either intravenous cisplatin or combination of methotrexate and celecoxib. It was found that median OS in the metronomic arm was superior than the chemotherapy arm (HR: 0.773; 95% CI: 0.65–0.97; $p = 0.026$) with a better toxicity profile in the metronomic arm. The choice of chemotherapy in the control arm is justifiable as no studies have shown a better OS with doublet chemotherapy over single chemotherapeutic agent.

Case 5

A 60-year-old male presented with history of tobacco consumption presented with an ulcerated lesion over the gingival sulcus for the last 4 months. On clinical examination, there was an ulceroproliferative lesion measuring 5 × 5 cm with matted cervical lymphadenopathy. Biopsy of the lesion revealed squamous cell carcinoma. Staging workup revealed multiple lung metastases. He was treated with a combination of cisplatin and 5FU for a total of 6 cycles. Unfortunately, he developed a progressive disease within 6 months. What are the options to treat the patient?

The choice of second line therapy depends upon the PS of the patient, prior systemic therapy, platinum free interval, and most importantly the financial status. Platinum-free interval (PFI) is defined as the time interval between the last platinum-based therapy to the development of disease progression. The time interval ranges from 3 to 6 months as mentioned in different clinical trials.[29,30] Those who have a PFI of more than 3 months can be rechallenged with platinum-based therapy. The treatment options are discussed as follows:

A. *Systemic chemotherapy*

In patients with PFI of more than 6 months, patients can be rechallenged with platinum-based therapy either alone or in combination with doublet-based chemotherapy.[9,31] Another option is to give low-dose metronomic chemotherapy with methotrexate and celecoxib as it has shown superior survival over cisplatin.[7]

Patients who had shorter PFI are deemed to be defined as platinum resistant and carry a poor prognosis. Agents that have been tried are docetaxel and methotrexate. Response rates and OS are very modest and there was no survival advantage over one another.[32]

B. *Cetuximab*

In patients with no prior exposure to cetuximab and with PFI of more than 6 months, they can be treated with cetuximab along with platinum doublet therapy.[5]

Cetuximab has been used either as a single agent or in combination with platinum in patients with shorter PFT in small phase II studies. As a single agent, response rate is around 13% with a median OS of 178 days.[33] Cetuximab has been tried in combination with platinum in a platinum resistant population. The response rates were almost similar to cetuximab monotherapy.[34]

C. *Immunotherapy*

Before the advent of immunotherapy as a first-line therapy in metastatic HNSCC, they were tried in recurrent second line settings and the results were very encouraging.

Both pembrolizumab and nivolumab have received U.S. Food and Drug Administration approval for usage in the second line setting.

Pembrolizumab anti-PD1 inhibitor was compared with nonplatinum agents in platinum resistant cases in KEYNOTE-040 trial.[30] There was an OS advantage in the whole population with pembrolizumab over the controlled arm (HR: 0.8, 0.65–0.98; $p = 0.016$), but mainly in patients with PDL1 $\geq$ to 50% (HR: 0.53; 0.35–0.81), the response rates with pembrolizumab were modestly superior than the control arm with lesser incidence of adverse events in the pembrolizumab arm compared with the control arm (13 vs. 36%, respectively).

Nivolumab was also used in a similar way in platinum resistant cases in phase III checkmate 141 trial.[29] The primary endpoint was again OS. The trial met its primary in point of improvement of OS from 5.1 to 7.5 months with the use of nivolumab (HR for death, 0.70; 97.73% CI: 0.51–0.96; $p = 0.01$), and the 1-year survival was 36 vs. 16.6%. This trial again established the role of immunotherapy by improving OS in the second line.

Durvalumab, an anti PDL1 inhibitor, has also been tried in recurrent metastatic HNSCC. In a single-arm phase II study, there was a response rate of around 16% with OS of 7.1 months.[35] Durvalumab was compared alone or in combination with tremelimumab with standard systemic therapy in phase III study but it failed to show any benefit over standard systemic therapy.[36]

D. *EGFR Tyrosine Kinase Inhibitor*

EGFR tyrosine kinase inhibitors like gefitinib and afatinib have been used in platinum resistant settings. Gefitinib

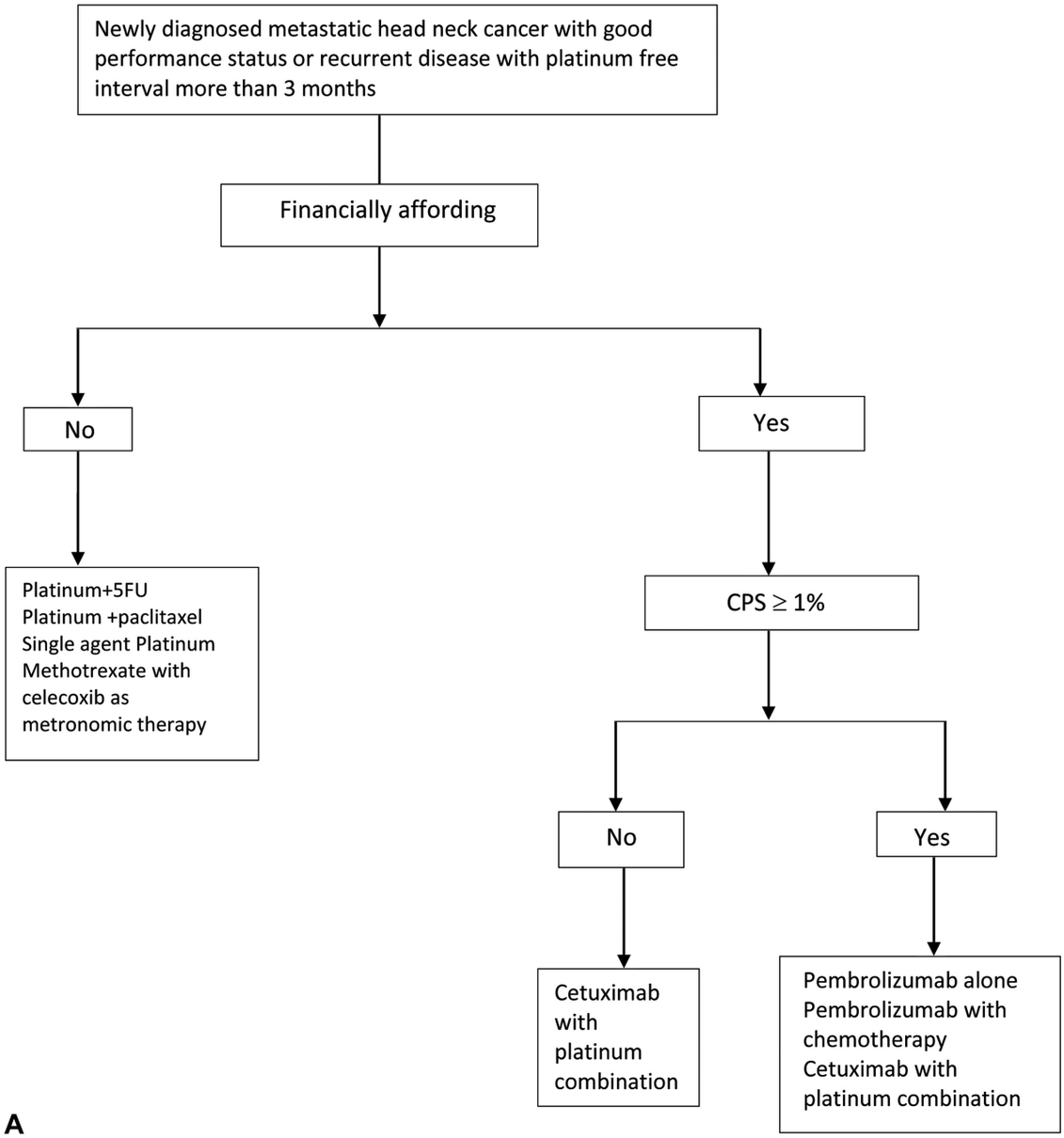

Fig. 1 (A, B) Algorithm regarding first-line treatment in newly diagnosed/-platinum-sensitive recurrent metastatic head neck cancer.

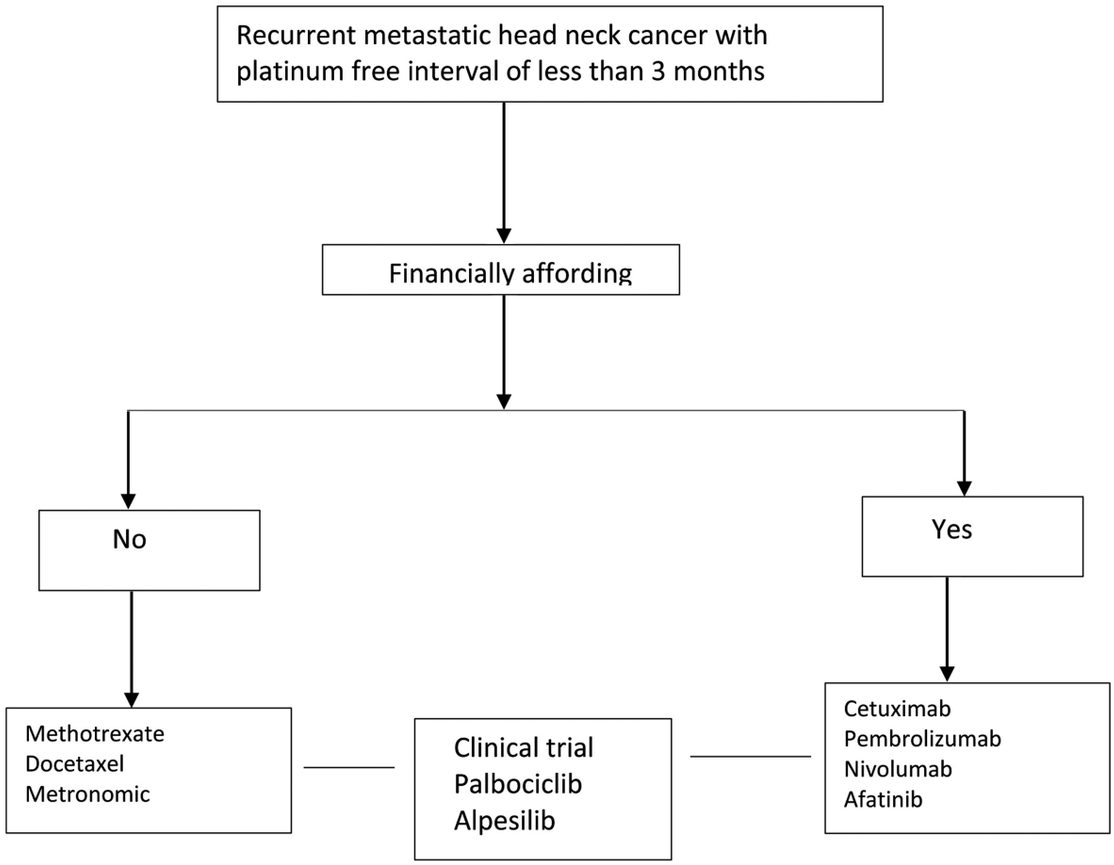

Fig. 1 (*Continued*)

did not improve either the response rate or survival compared with single-agent methotrexate.[37] Afatinib was compared with intravenous methotrexate (40 mg/m^2/week) in a phase III randomized trial involving Asian patients who had the disease progression following first-line platinum-based chemotherapy.

Out of the 340 randomized patients, afatinib significantly decreased the risk of progression or death by 37% versus methotrexate (HR: 0.63; 95% CI: 0.48–0.82; $p = 0.0005$; median 2.9 vs. 2.6 months). The response rate was 28% with afatinib versus 13% with methotrexate.[38] Another EGFR tyrosine kinase inhibitor erlotinib has been tried in combination with celecoxib and methotrexate as a metronomic therapy in platinum resistant oral cancers. The 3 month PFS was 71.1% and the 6 month OS was 61.2% with a response rate of 43%.[39]

E. *Newer therapies*

The field of recurrent metastatic head and the cancer is evolving fast with newer developments largely based on molecular pathways. Similar pathway is the CDK4/6 pathway. The CDK 4/6 inhibitor palbociclib has been investigated in phase I and II trials. In a phase II trial in combination with cetuximab, the objective response rate was 39% in the platinum resistant group.[40,41] Buparlisib 100 mg once daily, a phosphoinositide 3 kinase (Pi3K) inhibitor, was combined with paclitaxel versus paclitaxel alone in the phase II randomized BERIL 1 trial. There was an absolute 1.1-month PFS benefit in the combination arm (HR: -0.65; 95% CI: 0.45–0.95; $p = 0.01$).[42] Alpelisib is also being studied actively in such patients.[43]

Armamentarium of systemic therapy in metastatic HNSCC has been steadily increased over with the addition of monoclonal antibodies including IO. The response rate and survival advantage is still modest despite being statistically significant. Unfortunately, many of the therapies are still out of the reach for the common people depriving them to get these newer therapies. The therapeutic modality should be tailored and we proposed algorithm as shown in ►**Fig. 1A** and **B**, respectively.

Case 6

A 25-year-old female from Manipur presented with painless lump over both side of her neck with nasal obstruction since last 3 months. It was neither associated with any fever, cough, night sweats nor any other systemic symptoms. On clinical examination, there was 3 × 4 cm lymph node at right level III and multiple neck nodes max. 3.5 cm in greatest dimension at left level II, III, and IV region. On nasal endoscope, there was mass lesion arising from fossa of Rosenmollar extending right posterior nasal cavity. Biopsy from the mass lesion revealed nonkeratinizing squamous cell carcinoma, undifferentiated

subtype; the tumor cells were positive for p63 and cytokeratin.

Tumor cells are POSITIVE for Epstein–Barr virus encoded RNA (EBER-ISH) consistent with nasopharyngeal primary. Magnetic resonance imaging neck showed 6 × 4.5 cm mass arising from fossa of Rosenmollar with obliteration of left parapharyngeal fat and extending into anterior nasal cavity; without any intracranial extension, enlarged bilateral level II, III, IV, and V cervical nodes maximum dimension 5.2 cm with small right retropharyngeal node. Positron emission tomography computed tomography (PET CT) did not reveal any other metabolically active disease noted elsewhere. After 8 months of completion of her treatment, PET CT showed multiple lung metastasis; she was otherwise fit and symptomatic for her lung metastasis. How to treat the patient?

Nasopharyngeal cancer (NPC) is a malignancy with highly curative potential; skewed geographical distribution and mostly present among younger population with locally advanced stage. Infection with EBV is an important etiological factor particularly in nonkeratinizing and undifferentiated subtype. Workup for NPC should include EBV testing from both tumor and the blood. The method of detection of EBV in tumor includes In situ hybridization (ISH) for EBV encoded RNA (EBER) and IHC staining for LMP1.[44,45] Real-time polymerase chain reaction is used to evaluate EBV DNA load in plasma or serum and used as a marker for residual diseases monitoring. A meta-analysis showed that pretreatment plasma EBV DNA levels were independent prognostic factors for mortality and distant metastasis.[46]

Patients with early stage T1N0 M0 NPC should be treated with definitive radiation alone with local control rate around 90%.[47] For loco regionally advanced stage, the Intergroup trial 099 showed highly significant survival advantage favoring combined modality with cisplatin-based chemotherapy and radiation.[48] Asia-specific phase III randomized controlled trails (RCTs) confirmed that 5 years OS was around 70% for the chemoradiation compared with RT alone.[49] Subsequently, an individual patient-based meta-analysis of eight RCTs showed an absolute benefit in OS and EFS at 5 years with highest benefit resulting from concomitant chemoradiation rather than neoadjuvant or adjuvant chemotherapy.[50] A network meta-analysis (including 20 trials and 5,144 patient) showed that addition of adjuvant chemotherapy to chemoradiation was associated with better PFS compared with chemoradiation alone.[51]

Meta-analysis established the role of induction chemotherapy followed by chemoradiation is another standard of care in node-positive diseases.[52] Gemcitabine and cisplatin are preferred induction regimen, whereas for EBV-associated diseases modified TPF (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2, 5FU 600 mg/m^2 CI for 5 days) is preferred regimen.[53,54]

For metastatic NPC, there is limited options for systemic therapy and enrolment in a clinical trials is preferred. Gemcitabine plus cisplatin is the preferred first-line chemotherapy regimen demonstrated survival advantage compared with Cisplatin plus 5FU.[55] The role of cetuximab in combination with platinum salts tested in a phase II trial with acceptable safety profile in heavily pretreated patients.[56] The role immune checkpoint inhibitors like pembrolizumab (KEYNOTE-028) and nivolumab (NCI 9742) were tested in phase I/II trials, but the results were not so encouraging.[57,58]

Conflict of Interest

None declared.

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Enhancing Hospitalized Patients' Palliative Care Referrals via Machine Learning-Based Predictive Modeling within Electronic Health Record Systems

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Abstract

Access to palliative care (PC) holds significance for hospital-admitted patients grappling with the symptoms of life limiting illnesses. Nonetheless, numerous such patients who could gain from PC fail to receive it promptly or even at all.

We can leverage the prior year's historical data extracted from electronic health records of hospitalized patients to train a machine learning (ML) model. This model's purpose would be to prognosticate the requirement for PC consultation using real-time data. The model, operating as a semi-supervised system, will be integrated into institutional data pipelines, and utilized by a downstream display application overseen by the PC team. In cases where the PC team deems it suitable, a team member will communicate with the respective care team of the patient. The ML model's training efficacy will be assessed using the area under the curve (AUC) metric, employing a 20% reserved validation set. The threshold for PC consultations will be grounded in historical data. To enhance the ML model's precision, the pivotal variables within the model will be pinpointed, and any sources of biases or errors in the model will be identified for meticulous refinement. The AUC values of successive ML models will be juxtaposed with cross-validation data.

Automatizing the referral procedure through electronic health record systems has the potential to usher in a more effective and streamlined approach to healthcare delivery.

Keywords

- hospitalized patients
- palliative care referrals
- machine learning
- predictive modeling
- electronic health records

Introduction

In recent years, there has been a growing recognition of the importance of palliative care (PC) in improving the quality of life for hospitalized patients with serious illnesses. PC focuses on providing relief from symptoms, pain, and stress, aiming to improve the overall well-being of patients and their families. However, despite its significant benefits, there is a notable gap in the timely identification and referral of patients who could benefit from PC services.[1]

To address this challenge, there is an emerging opportunity to leverage the power of machine learning (ML)-based predictive modelling within electronic health record (EHR) systems.[2] By harnessing the vast amount of patient data stored in EHRs, it is possible to develop predictive models that can identify hospitalized patients who are most likely to benefit from PC interventions.

This concept article aims to explore the potential of using ML techniques to enhance the referral process for PC within hospital settings. By integrating predictive models into EHRs,

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healthcare providers can identify patients who may benefit from early PC interventions, allowing for more proactive and personalized care planning. In contrast to prior methods, this strategy aims to directly forecast PC consultations instead of relying on mortality as an indirect measure. The outcomes of the model can subsequently be incorporated into the procedures of the PC team.

This article will first provide an overview of the current challenges in PC referrals and the potential benefits of leveraging ML algorithms in addressing these challenges. It will then discuss the key components and considerations involved in developing a ML-based predictive model for PC referrals, including data collection, feature selection, model training, and evaluation. Furthermore, ethical and privacy considerations will be examined, as the use of patient data in predictive modelling raises important concerns regarding confidentiality and informed consent. This article will propose strategies to mitigate these concerns and ensure the responsible and ethical use of patient data. Finally, this concept article will highlight potential implementation challenges and opportunities, as well as the expected impact of integrating ML-based predictive modelling into EHRs for PC referrals.

Overview of the Current Challenges in PC Referrals and the Potential Benefits of Leveraging ML Algorithms

PC referrals face several challenges within hospital settings, resulting in delayed or missed opportunities for patients to receive the appropriate care. Some of the key challenges include subjective patient identification reliant on healthcare providers' assessments, delayed referrals, lack of standardized referral criteria, and resource constraints.[3] Leveraging ML algorithms within EHRs offer promising opportunities to address the challenges in PC referral triggers, which could include diagnosis of life-limiting or terminal illnesses (e.g., advanced cancer, end-stage heart failure), severe and progressive symptoms (e.g., uncontrolled pain, dyspnea), frequent hospitalizations and readmissions, decline in functional status and quality of life, and limited response to curative treatments.[4–8] Some potential benefits include early identification and intervention by analyzing patient data available in EHRs, objective and standardized referral criteria, enhanced accuracy and efficiency, and personalized care planning as ML models can consider a wide range of patient characteristics, such as medical history, comorbidities, and PC needs assessment like physical assessment of symptoms (pain, nausea, fatigue), psychosocial assessment (emotional distress, spiritual concerns), discussion of patient's goals, values, and preferences, and assessment of family and caregiver needs to develop personalized care plans.[2,9]

Clinical Use Case Design

The intended model aims to predict consultations with PC for patients during their hospitalization. This prediction will facilitate prompt PC availability, potentially enhancing the satisfaction of both patients and caregivers with the healthcare provided. The model will operate as a web-based service, integrated with institutional data flows, and utilized by a subsequent display application overseen by the PC team. For those patients that the PC team deems appropriate, a team member will then contact the patient's corresponding care team. Stakeholders will be engaged when designing the solution (both for buy-in and support and for end-user design) and will include hospital administration, non-PC healthcare teams, medical informatics, the information technology team, patients/caregivers, and funders. Outcomes of enhanced PC referrals would include improved symptom management and pain control, enhanced patient and family satisfaction, better alignment of medical care with patient values and preferences, reduced hospital readmissions and emergency department visits, and enhanced communication and coordination among healthcare providers.[9] Often these might lead to cost savings through reduced hospitalizations, decreased utilization of expensive interventions, improved resource allocation and healthcare efficiency, and enhanced patient and family satisfaction leading to better reputation for the hospital.[10,11]

Design Thinking Methodology

We will start with involve the users to understand the needs and challenges of the stakeholders involved, including patients, caregivers, healthcare providers, and PC specialists via interviews, surveys, and observations to gain insight into their experiences and pain points. We will ideate solutions via brainstorming over a wide range of workable solutions to the problem, without worrying about feasibility at this stage, via mind mapping, brainstorming sessions, and SCAMPER (Substitute, Combine, Adapt, Modify, put to other uses, Eliminate, Rearrange) to generate ideas,[12] and diverse perspectives and challenges to assumptions will be encouraged at this stage. Next step involves developing a rough prototype of a web application, using wireframes, sketches, or low-fidelity mock-ups. We will perform user testing to get feedback on prototypes using techniques like A/B testing or surveys to get quantitative data on user preferences.[13] We will institute necessary changes based on the feedback to the web application and repeat the prototyping and testing process until we have a final product that meets the needs of users and achieves goals.

Data and Pre-Processing

We will get the necessary permission to collect hospital data for 1 year, for adults (>18 years), and inpatients, excluding patients in the PC unit or waiting to be transferred to an external hospice. The data category will encompass numeric, categorical, or binary formats contingent upon the nature of the variable. Instances consist of patient demographic information, past utilization (quantified by tallying recent instances of inpatient care, intensive care, and primary care interactions before admission), concurrent health conditions (ICD11 diagnosis codes), and dynamic data like lab results and the ongoing length of stay.

Data Ingestion and Preprocessing

In the existing framework of system architecture, whenever a modification is applied to EHRs, the system initiates the creation of HL7 messages. These messages are then disseminated within the organization through the Enterprise Service Bus(ESB) version.[14] The ESB is subject to ongoing surveillance by the Project Data Pipeline. This pipeline includes a rules manager designed to implement clinical enrichment rules onto the messages. The outcomes produced by this rules manager can encompass significant data required for the operation and presentation of the application. Alternatively, if necessary, it can also trigger predictive processing in situations where changes in pertinent variables for monitored patients come into play.

Model Development and Validation

We intend to create a semi-supervised learning framework by utilizing both labeled datasets and unlabeled outcomes.[15] Specifically, our focus is on developing a model that employs a Poisson distribution process to mathematically capture the concept of time-to-event outcomes, particularly in the context of PC consultations.[16] These consultations can be understood as events occurring at varying rates over time. Our approach involves utilizing a classification task with a decision tree algorithm.

To construct the response variable, we will measure the time from admission to a PC consult, taking into account that this measurement is right-censored at the discharge time. The Poisson process will enable us to predict the rate of PC interventions per unit of time. For practical implementation in a clinical setting, we will transform this rate into a 7-day probability of PC consultation. While various ML models can be employed that can leverage Poisson likelihood, our choice is the Gradient Boosting Machine (GBM). The GBM's ability to incorporate a loss function equivalent to the minus log-likelihood for Poisson distributions makes it well-suited for our purpose.

Furthermore, the GBM can effectively handle missing values, which is particularly important considering the presence of missing data in laboratory values and diagnosis codes. Our model will be dynamic, updating predictions as new information becomes available through a carry-it-forward dataset construction approach. However, it is important to acknowledge that assuming constant predictor values between observations might introduce bias or errors.

Upon exceeding a predefined threshold, the model will trigger notifications to the PC team. The threshold will categorize the 7-day probability of PC consultation as "low," "medium," or "high." The "high" category will be calibrated based on the existing capacity of the PC service, aiming to align with the average of around ten new consults daily, including those via the traditional pathway. This calibration will involve utilizing data to establish a threshold for the receiver operating characteristic (ROC) curve.

The labeled dataset will be divided into 80% for training and 20% for testing. We will determine hyperparameters for the GBM model—such as the number of trees, shrinkage, and interaction depth—through cross-validation. This process entails partitioning the dataset into random subsets, using one as the test set while training on the others. Repeating this process for each subset, the average results will guide our final choice of hyperparameters. We will employ 5- to 10-folds, depending on our computational resources. The optimal hyperparameters will be those producing the highest area under the curve (AUC) in the time-dependent ROC curve. This curve will plot AUC and positive predictive value.

Ultimately, the final model will be fitted using all available data and evaluated in real-time using unlabeled data. Its performance will be compared to the cross-validation data, allowing us to assess the AUC and make any necessary adjustments to the model.

User Validation and Clinical Integration

Validation metrics will include the number of PC consults triggered by the ML model, compared with previous years' data, and changes in clinical outcomes guided by the new ML model. End users will be internal stakeholders, to begin with, or external customers if successfully implemented. We will gather feedback from users within the time frame for testing and analyze patterns in the feedback and identify areas where the model can be improved. We will make improvements like adjusting the model parameters, collecting additional data, or making changes to the user interface. We will repeat the process until satisfied with the performance of the ML model.

We will identify key stakeholders who will be impacted by the introduction of the ML model, such as clinicians, administrators, patients, and IT staff. Engage with them early in the process to understand their needs and concerns and involve them in the decision-making process. We will clearly articulate the benefits of the ML model to stakeholders like increasing efficiency, reducing costs, and enhancing the quality of care. We will anticipate and address concerns and potential risks associated with the introduction of the ML model. Communicate clearly about the safeguards and measures in place to protect patient privacy and data security. Provide evidence-based information to address concerns about the accuracy and reliability of the model. We will provide adequate training and support to stakeholders to ensure they are comfortable with the technology and understand how to use it effectively. Offer ongoing support to address any issues or questions that may arise. We will monitor and evaluate the implementation of the ML model to ensure it is meeting the desired outcomes and identify areas for improvement. Share the results with stakeholders to demonstrate the impact of technology and foster ongoing support and engagement.

Ethics, Legal, and Regulatory Considerations

Transparency: It is important to ensure that the ML application is transparent in how it makes its decisions. Patients and healthcare professionals need to be able to understand how the algorithm arrived at its recommendations, so they can

trust and act upon them. This holds significant significance in the context of end-of-life choices. To illustrate, comprehending and explaining the course that a decision tree follows to arrive at its conclusion is straightforward, whereas tracing the trajectories of numerous trees, numbering in the hundreds or thousands, becomes notably more challenging.

Autonomy: The ML application should not replace the judgment of healthcare professionals. It should be designed to support clinical decision-making, rather than replace it. It is up to the healthcare professional to make decisions about the care of their patients.

Accountability: It is important to ensure that the ML application is accountable for its decisions. This means that there should be mechanisms in place to monitor its performance and identify any errors or biases that may arise.

Informed consent: Patients should be fully informed about the use of ML in their care and should have the option to opt out if they choose. This requires clear communication about how the ML application works and the implications of its recommendations.

Privacy: The use of personal data is essential for ML algorithms to work, which can potentially reveal sensitive medical information about patients. Therefore, it is important to ensure that patient privacy is protected throughout the development, deployment, and use of the ML application.

Discussion and Conclusion

This concept article aimed to explore a project utilizing the potential of ML-based predictive modelling within EHRs to enhance the referral process for PC in hospitalized patients, allowing for timely and appropriate referrals. The accuracy and performance metrics achieved by these models will suggest if they have the potential to significantly improve the current referral process. Proactive identification of patients who may benefit from PC can initiate early conversations and interventions, leading to better patient outcomes and enhanced quality of life.

One of the key advantages of using ML in this context would be the ability to leverage a wide range of patient data, including demographics, clinical variables, laboratory results, and diagnostic codes. These models can detect patterns and associations that may not be apparent to human clinicians, enabling more accurate predictions. Furthermore, the models can continuously learn and adapt from new data, refining their predictions over time and improving their performance.

However, several challenges and limitations need to be addressed before implementing ML-based predictive modelling for PC referrals in electronic health systems.

Primarily, ensuring data quality and standardization across different healthcare settings is crucial. Discrepancies, absent information, and mistakes within EHRs can result in prejudiced or erroneous forecasts, posing a potential risk to patient well-being. To illustrate, the training of the model will utilize a historical cohort of primary care consultations that is not flawless; specifically, numerous individuals who could have gained from a primary care consultation might not have undergone one. This disparity has the potential to cause oversights by the algorithm, especially if there exists a consistent bias towards primary care consultations under the existing protocols. Mitigation strategies may include effort to get better representative data, using metrics like precision, recall, F1 score, adjust class weights, fairness constraints in model training, regular model audit, and monitoring. Therefore, data preprocessing and quality assurance processes must be robustly implemented.

An additional obstacle pertains to the comprehensibility of ML models. Despite their ability to attain remarkable predictive precision, these models frequently lack transparency in elucidating the fundamental decision-making process. This absence of clarity could impede the establishment of trust and approval from healthcare experts. To illustrate, consider the presumption of carrying forward data for time-dependent predictors, where the assumption that a patient's hemoglobin level remains constant for 3 days solely because a laboratory test was conducted on a Monday and not repeated until Thursday does not hold true. The advancement of interpretable ML techniques, capable of offering insights into the drivers behind predictions, is a domain that demands further attention.

Additionally, ethical considerations must be carefully addressed when implementing ML models in healthcare. Patient privacy, data security, and informed consent are of utmost importance. Safeguards must be in place to protect sensitive patient information and ensure compliance with privacy regulations. It is crucial to strike a balance between the potential benefits of predictive modelling and the ethical responsibilities associated with its use. Should our solution become part of a clinical workflow, obtaining approval from the Food and Drug Administration (FDA) could be necessary. For instance, the US FDA categorizes medical devices, including software, into four different classes, depending on the level of risk they pose to both the patient and the user.[17]

Despite these challenges, the potential impact of ML-based predictive modeling in enhancing PC referrals within EHRs is significant. Future research should focus on prospective validation of the models in real-world clinical settings to assess their performance in diverse patient populations. Additionally, studies should explore the impact of implementing these models on clinical workflow, patient outcomes, and healthcare resource utilization.

Furthermore, collaboration between clinicians, data scientists, and policymakers is essential for successful implementation. Engaging healthcare providers in the development and validation of these models can help address concerns, foster trust, and ensure that the technology aligns with clinical needs and workflows. Moreover, policymakers should establish guidelines and regulations that promote the responsible and ethical use of ML in healthcare.

In conclusion, the use of ML-driven predictive modeling shows significant potential in improving the process of referring patients for PC during their hospitalization. Detecting individuals who could gain from PC at an earlier point can result in better patient results and more effective utilization of resources. Nevertheless, it is crucial to meticulously address concerns related to data accuracy, comprehensibility, and

ethical implications. By tackling these obstacles and delving deeper into the possible advantages, we can make strides in incorporating ML into EHRs, thereby enhancing the provision of PC for those requiring it most.

Patient Consent
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Conflicts of Interest
None declared.

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Factors Associated with Choosing the Kerala Model of Palliative Care versus Standard Care among Indian Cancer Patients

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Abstract

Patients who opt for the Kerala Model of Palliative Care (KMPC) report favorable psychological outcomes. Still, not all patients in Kerala prefer this treatment's approach. Hence, this study is aimed to examine the demographical, medical, pain, and psychological factors associated with cancer patients who choose the KMPC versus standard care (SC). Using a cross-sectional design and purposive sampling, 87 patients (SC = 40; KMPC = 47) residing in Kerala, India, responded to questionnaires on pain, anxiety, and depression, and quality of life (QoL). Data analysis was conducted using chi-squared and independent sample *t*-tests. Findings revealed that KMPC (vs. SC) patients had lower levels of education, were self-employed or homemakers, belonged to a middle or low socioeconomic status, received government aid or were financially self-supported, and were diagnosed for less than 1 year or less than 5 years. KMPC patients reported higher levels of pain, lower levels of anxiety and depression, better overall total QoL, physical health, social health, functionality capacity, and emotional health. These findings suggest the need for community awareness programs regarding the benefits of opting for the KMPC. Patients who chose KMPC reported higher levels of pain than SC patients, highlighting the need for the KMPC to improve its approach to pain management.

Keywords
- palliative care
- pain management
- quality of life
- India

Introduction

Palliative care aims to provide relief from pain and suffering and improve patients and their caregivers' quality of life (QoL).[1] Passed as a public health policy in Kerala, India, in 2008, the Kerala Model for Palliative Care (KMPC) aims to provide patients with optimal support and care throughout the cancer trajectory.[2] The model has a three-tier structure: (i) community and primary health centers offer medical and supportive care, (ii) a team of medical (physicians, nurses) and nonmedical (social workers, counselors) staff provide weekly at-home care, and (iii) government-certified trainers host capacity and skill-building workshops and training sessions for community volunteers and medical staff.[3] Typically, physicians introduce patients to KMPC when diagnosed with a life-threatening or terminal illness,[2] offering assurances that standard care (SC) will be given as well and explaining that KMPC aims at providing holistic (e.g., psychological, spiritual, social), at-home care as per the preferences and needs of the patient, irrespective of the stage of their illness.[4]

Research has shown that this community-based KMPC provides a range of practical (e.g., wound dressing, free

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medication, financial support for the family) as well as psychosocial (e.g., psychoeducation, counseling) support for patients and their families.[3] Further, patients who availed the KMPC reported feeling more independent, self-reliant, and self-confident.[4] Yet, many cancer patients do not choose KMPC and continue to opt for SC.[2] While the factors of physicians, patients, and family might impact this decision, this study focuses only on patient factors.

Understanding the factors associated with choosing KMPC/SC might guide intervention efforts to assist patients in making informed choices about the type of care they prefer. To the best of our knowledge, no research in India has examined the differences between patients who choose KMPC versus SC.

Therefore, the current study examines the demographical, medical, pain, and psychological factors associated with patients residing in Kerala who selected KMPC or SC.

Methods

Study Design and Participants

Using a cross-sectional design and purposive sampling (to ensure an equal number of patients who had chosen KMPC versus SC were represented in the sample), 87 patients (SC = 40; KMPC = 47) diagnosed with any cancer and at any cancer stage were recruited from 5 hospitals in Kerala. Inclusion criteria for the patients were that (i) they are at least 18 years of age, (ii) could speak Malayalam (regional language), (iii) were aware of their diagnosis, and (iv) did not have any other comorbidities or psychiatric conditions (as reported by themselves). All procedures performed in the study involve human participants were in accordance with the ethical standards of the Indian Institute of Technology Hyderabad [IITH/IEC/2018/03/19 w.e.f 14/03/2018] and with 1964 Helsinki declaration and its later amendments or comparable ethical standards. Further, approval was provided by the medical officers of the hospitals involved in the study.

Procedure

Eligible participants were approached by the first author (PG) at the oncology departments (SC patients) or the palliative care department within a hospital (KMPC patients)^. Participants were introduced to the study, including a brief description of the study and the time it would take the patient to participate. If any patient expressed an interest in participating, PG elaborately explained the study details and answered any questions that the patient had regarding the study. Following this, written informed consent was obtained from the participants, their demographical and medical information were collected, and the questionnaires were administered by PG.

One hundred and two patients were approached (SC = 52; KMPC = 50) by PG, of whom 15 declined participation (SC = 12; KMPC = 3) citing the following reasons: (i) caregivers refused patient's participation (commonly, in India, family caregivers play a considerable role in medical decision-making),[5] (ii) lack of time, (iii) too tired to participate, (iv) wanted the researcher to provide an incentive for participation which was not within the scope of this study, or (v) desired privacy. These reasons suggest that SC patients were less willing to participate in the study, warranting further attention. Consequently, the total number of participants for this study was 87 (SC = 40, KMPC = 47).

Measures

Pain[6]: Pain was assessed using a 11-point self-reporting Numeric Rating Scale, with the values of 0 representing "no pain" and 10 representing "worst pain imaginable."

Anxiety and depression (Hospital Anxiety Depression Scale (HADS)[7]: The HADS is a 14-item Likert scale that assesses psychological distress in nonpsychiatric patients and consists of 2 sub- scales of anxiety (7 items) and depression (7 items). The HADS has been used extensively in Indian cancer populations and reports good validity and reliability.[5,8,9] The Cronbach α score for the current study is 0.805, indicating a good reliability.

Quality of life (Functional Assessment of Cancer-General; FACT-G)[10]: The FACT-G is a 27-item Likert scale designed to measure four domains of health-related QoL in cancer patients, namely physical (7 items), social (7 items), emotional (6 items), and functional well-being (7 items). The FACT-G has been used in Indian cancer populations and reports good validity and reliability.[11–13] The Cronbach α score for the current study is 0.789, indicating a good reliability.

Analysis

To differentiate between the KMPC/SC groups, chi-squared test was used for the demographic and medical variables, which were categorical in nature. Independent sample *t*-tests were conducted for the psychological variables, which were continuous in nature.

Results

Participants' Characteristics

KMPC patients ($n = 47$; mean age = 48.2 years) were primarily male, married, had an undergraduate degree, in Stage IV of cancer, and were diagnosed with cancer for between 1 and 5 years. SC patients ($n = 40$, mean age = 50.2 years) were primarily male, married, in Stage IV of cancer, and diagnosed with cancer for less than 1 year. ►**Table 1** describes patients' demographical and medical details per group.

Differences between the KMPC and SC Patient Groups

Significant differences between patients who chose KMPC versus SC were found with KMPC patients reporting higher levels of pain, lower levels of anxiety and depression, better overall total QoL, physical health, social health, functioning capacity, and emotional health. ►**Table 1** shows the results of group comparisons between the demographic, medical, and psychological outcomes.

Discussion

This study aimed to examine the factors that differentiated cancer patients who chose KMPC over SC residing in Kerala,

Table 1 Patients' details and comparisons between the KMPC and SC patients

Variables		Treatment style				Test statistics	
		SC		KMPC			
		n	%	*n*	%	X^2	*p*-Value
Gender	Male	23	57.5	31	65.9	0.657	ns
	Female	17	42.5	16	34.1		
Marital status	Unmarried	0	0	2	4.2	3.31	ns
	Married	39	97.5	41	87.3		
	Widowed	1	2.5	4	8.5		
Religion	Hinduism	20	50	24	51.1	2.67	ns
	Christianity	11	27.5	7	14.9		
	Islam	9	22.5	16	34		
Caste	SC/ST[a]	1	2.5	4	8.5	1.74	ns
	OBC[b]	14	35	13	27.6		
	General	25	62.5	30	63.9		
Education	Illiterate	0	0	3	6.38	17.39	0.05
	Until 5th grade	0	0	6	12.7		
	10th grade	8	20	13	27.6		
	12th / diploma	2	5	8	17		
	Undergraduate degree	22	55	14	29.7		
	Postgraduate degree	8	20	3	6.3		
Occupation	Government	9	22.5	3	6.4	16.63	0.05
	Private	12	30	8	17		
	Business	3	7.5	4	8.5		
	Self	4	10	16	34		
	Homemaker	4	10	12	25.5		
	Student	4	10	3	6.4		
	Retired	4	10	1	2		
Socioeconomic status	Low	8	20.9	15	31.2	6.93	0.05
	Middle	15	37.5	24	51		
	High	17	42.5	8	17		
Source of financial support	Self	25	62.5	22	47	7.86	0.05
	Government	3	6.3	15	31		
	Private	12	25.5	10	22		
Stage of cancer	Stage I	3	7.5	11	23.4	5.74	ns
	Stage II	14	35	11	23.4		
	Stage III	10	25	7	14.8		
	Stage IV	13	32.5	18	38.2		
Time since diagnosis	<1 year	23	57.5	19	40.4	6.50	0.05
	<5 years	17	42.5	22	46.8		
	>5 years	0	0	6	12.8		
Family history of cancer	Parents	2	5	2	4.3	6.43	ns
	Siblings	1	2.5	3	6.3		
	Relatives	10	25	3	6.3		
	No history	27	67.5	39	82.1		

Table 1 (*Continued*)

Variables		Treatment style				Test statistics	
		SC		KMPC			
		n	%	*n*	%	X^2	*p*-Value
		Mean	SD	Mean	SD	T	*p*-Value
Age (years)		50.2	10.4	48.2	8.7	−0.506	ns
Pain		2.35	1.64	2.89	1.56	−1.57	0.05
Anxiety and depression	Anxiety	9.98	4.41	8.21	4.11	1.91	0.05
	Depression	7.93	4.17	7.32	4.89	0.623	0.05
	Total	17.65	8.15	15.32	8.10	1.33	0.05
Quality of life	Physical well-being	16.25	5.30	17.44	5.24	−1.05	0.05
	Social well-being	13.30	3.17	16.25	3.78	−3.96	0.01
	Emotional well-being	12.45	4.01	14.14	4.40	−1.88	0.05
	Functional well-being	10.32	3.05	12.55	4.51	−2.72	0.05
	Total	52.32	10.92	60.40	14.86	−2.91	0.05

Abbreviations: KMPC, Kerala Model of Palliative Care; ns, not specified; SC, standard care; SD, standard deviation.
[a]SC = scheduled caste/ST = scheduled tribe.
[b]OBC = other backward caste.

India. KMPC patients were found to have lower levels of education, were self-employed/homemakers, belonged to a low or middle socioeconomic status, used government aid or personal finances for their cancer-related expenses, and were diagnosed with cancer for either less than 1 year or for 5 years as compared with SC patients. Taken together, these variables are either directly or indirectly linked to one's financial background.[14] Therefore, factors determining the patient's financial ability may have differentiated between the two groups in this study. Furthermore, despite the positive psychosocial outcomes of utilizing the KMPC,[4] patients may negatively perceive it as a facility for the poor and needy, thus misunderstanding the cost-effective aspects of this model of care.[4] Consequently, in the current study, those who could afford cancer treatment expenses may have chosen SC.

KMPC patients had higher levels of pain than SC patients in this study. Most KMPC patients were diagnosed for 5 years. Therefore, the long and exhausting treatment for cancer may have increased KMPC patients' pain.[15] These findings align with existing western research reporting that patients who receive hospice or PC care report higher pain levels,[16] indicating that patients may have chosen KMPC to alleviate their high levels of pain or as a more appropriate method of pain management as opposed to their SC counterparts who reported lower levels of pain. It is also possible that the KMPC approach was not optimally managing the patient's pain bearing capacity as compared with SC treatment. Indeed, despite being the largest producer and exporter of opioids and 5.4 million Indians requiring palliative care every year, India offers less than 1% of its population access to reliable and sustainable sources of morphine for pain relief.[3]

In the current study, patients receiving KMPC had lower levels of anxiety and depression than SC patients. These findings are in line with recent research from Kerala, wherein cancer patients reported high levels of anxiety due to the side effects of treatment.[17] Owing to the home-based, holistic care provision, the KMPC responds to the psychological distress patients undergo during treatment[3,16], while psychological support services are lacking/inadequate in Indian cancer hospitals.[17] This may explain why SC patients in the current study reported higher levels of anxiety and depression than their KMPC counterparts.

KMPC patients in this study reported higher levels of QoL and its subdomains of physical, emotional, social, and functional well-being compared with their SC counterparts. These findings add to existing literature indicating that palliative care improves QoL by preventing and relieving physical suffering by assessment, early identification, and pain treatment.[18] KMPC patients might have had better physical health and functional capacities because they were treated at home per the model's protocol, which may have allowed the patients increased autonomy to engage in household chores and activities.[15] This study found that the KMPC group experienced increased emotional fulfillment and stability than the SC group, contrasting with existing research, which identified high emotional distress or lowered emotional health among cancer patients undergoing palliative care.[19] This difference maybe because KMPC patients can be recruited into care at any stage of the treatment process rather than only when the patient is at the terminal stage or on the deathbed,[4] as opposed to traditional palliative care provision worldwide.[20] Therefore, patients choosing KMPC may be better emotionally adapted to cancer and its treatment. In addition, the current study found that patients from the KMPC group had increased positive social interactions as opposed to their SC counterparts. The unique community-owned, home-based approach of care practiced in the KMPC is reported to significantly improve the patient's family well-being, enhance the

patient's social network, increase the community's understanding, and ability to support the patient.[3]

Implications

Although patients who selected the KMPC reported lower anxiety and depression and improved QoL, they experienced higher levels of pain than their counterparts receiving SC in this study. These findings suggest that the KMPC may need to improve access to and utilization of pain relief medication, such as morphine, prevalent in India.[18] Therefore, future research should explore meticulously the barriers and facilitators to pain management among patients choosing the KMPC. Further, the current study revealed that patients' financial background might play a role in their preference of KMPC over SC, indicating the need to reduce the stigma associated with their opting for KMPC. This can be done by raising community awareness of KMPC to sensitize and educate the wider public of the possible psychological benefits to patients who use these services. Further qualitative research to explore this aspect could increase our understanding of this issue.

Strengths and Limitations

The current study has many strengths. First, to our knowledge, this is the first study that attempted to compare cancer patients who selected the KMPC or SC. Second, this study explored a range of psychological variables that may be associated with the choice of treatment style, thereby providing a broader understanding of factors that differentiate between the KMPC and SC groups. Third, by using purposive sampling, this study was able to recruit a comparable and representative sample per group, thus allowing meaningful interpretations of the findings.

These strengths notwithstanding, this study has some limitations. First, multiple stakeholders (e.g., family, physicians) who might play a role in selecting treatment style were not included. Second, owing to the study's cross-sectional design, it is difficult to assess whether there were any changes in patients' group membership. Therefore, future research should use a longitudinal method to trace any changes over time. Third, more SC (vs. KMPC) patients declined participation in this study. Given the reasons for nonparticipation, some suggestions to overcome this issue for future research are (i) sharing/keeping study's information in accessible yet discrete locations for potential participants to read at their convenience, (ii) underscoring that interviews can take place telephonically thereby addressing privacy concerns, and (iii) using a physician/healthcare worker referral system wherein they identify eligible patients who may otherwise decline participation (e.g., due to increased distress) and inform them about the study. Fourth, the sample size for the current study was small as the time duration for data collection was short and in-keeping with the academic schedule of the first author, PG. Therefore, due to the small sample size, generalization of the findings is not possible. Future studies need to include a larger sample to better understand the relationship between a range of variables and patients who choose either KMPC/SC.

Conclusion

This study reported that patients who choose KMPC belong to an overall lower financial status, have lower levels of anxiety and depression, higher levels of QoL and its subdomains, and higher levels of perceived pain compared with patients who choose SC. These findings highlight the need to improve the patient's pain management efforts by the KMPC professionals. Additionally, this study's findings indicate the need to reduce stigma related to selecting the KMPC by increasing wider community awareness and sensitivity to this treatment.

^Footnote

- SC consists of treatment protocols for a specific illness that are accepted and followed by the treating physician. In the case of this study, SC refers to the standard medical care protocols for the treatment of cancer that are followed by the oncologist.

Reference: Standard of care. National Cancer Institute of health. Accessed September 15, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/standard-of-care

- The hospitals where patients were recruited include:
  - Ernakulam General Hospital (total = 46; SC = 17; KMPC = 29)
  - Anwar Memorial Hospital (total = 12; SC = 5; KMPC = 7)
  - Lakshmi Hospital (SC = 8)
  - Government Hospital Aluva (total = 21; SC = 10; KMPC = 11)

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Authors' Statement

This manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each of the authors believe that the manuscript represents our honest work.

Authors' Contribution Details (ticked as applicable)

P.N.G. was involved in conceptualization, designing, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review. M.P.G. was involved in conceptualization, designing, definition of intellectual content, literature search, data analysis, statistical analysis, manuscript editing and review. S.C. was involved in definition of intellectual content, manuscript preparation, manuscript editing and review. M.C. was involved in definition of intellectual content, literature

search, manuscript preparation, manuscript editing and review. S.C. is guarantor for this manuscript.

Conflict of Interest
None declared.

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Double-Expressor Lymphoma in a Young Child—A Case Report and Review of Literature

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Abstract

Double hit lymphoma (DHL) and double-expressor lymphoma (DEL) are now considered as aggressive types of diffuse large B cell lymphoma. DHL is characterized by a dual rearrangement of MYC and B cell lymphoma 2 (BCL-2) and/or B cell lymphoma 6 (BCL-6) and DEL by overexpression of MYC and BCL-2. Both DHL and DEL have aggressive presentation and are more common in elderly population. We present a case of 1 ½ years old boy who presented with bilateral proptosis, and diagnosed as non-Hodgkin lymphoma with central nervous system involvement. Immunohistochemistry revealed high expression of MYC and BCL-2. Fluorescence in situ hybridization studies done to rule out DHL showed no translocation of C-MYC, Bcl-2, and Bcl-6 and hence were confirmed as double-expressor high-grade B cell lymphoma. Dual expression of C- MYC, Bcl-2, or Bcl-6 always needs further evaluation to rule out the more aggressive DHL subtypes.

Keywords

- child
- proptosis
- non-Hodgkin lymphoma
- double-expressor lymphoma

Introduction

Lymphomas with recurrent chromosomal breakpoints activating multiple oncogenes, and if MYC is one of them, are referred to as double hit lymphomas (DHL). Harboring a MYC rearrangement with a B cell lymphoma 2 (BCL-2) and/or B cell lymphoma 6 (BCL-6) rearrangement is now classified as high-grade B cell lymphoma.[1] Double-expresser lymphomas (DEL) and DHL are the new subsets of diffuse large B cell lymphoma (DLBCL) first described in 2016. DELs are DLBCL with increased expression of MYC and BCL-2 proteins by immunohistochemistry (IHC) but characterized by absence of detectable translocation by fluorescence in situ hybridization (FISH). Coexpression of MYC and BCL-2 proteins without underlying rearrangements is currently considered as a new adverse prognostic indicator. DHL and DEL are distinct biological entities associated with aggressive disease, high rates of central nervous system (CNS) involvement, and very inferior clinical outcomes to standard chemotherapy regimes. This subset of lymphomas is generally seen in elderly and is rarely reported in pediatric population. We report a case of 1 ½ years old male child who presented with bilateral proptosis with extensive disease with increased expression of c-Myc and Bcl-2. FISH studies ruled out DHL and confirmed the diagnosis of double-expressor high-grade B cell Lymphoma.

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Hence, FISH studies are essential to identify these from other DLBCL cases to prognosticate them and to administer intensive chemotherapy.

Case Report

A 1 ½ years old boy presented with complaints of progressive prominence of right eye for the past 1.5 months. There was no associated redness of eyes or discharge. The child did not have any complaints of irritability, vomiting, refusal to walk, decreased activity, fever spikes, abdominal distention, or white eye reflex prior to this episode. The parents gave a vague history of trivial trauma preceding the onset of symptoms. There was no family history of consanguinity.

On examination, the child had a right gross ab-axial proptosis with inferomedial globe dystopia associated with fullness of the right cheek. An ill-defined, firm, noncompressible, nontender mass was palpable in the superior, lateral, and inferior quadrant (►**Fig. 1**). Finger insinuation test between the orbital rims or the globe was negative. Child had mechanical right eye ptosis covering the visual axis. The child resisted occlusion of the left eye for near. Extraocular movement in the right eye was restricted in all gazes and direct light reflex revealed a relative afferent pupillary defect. A visual evoked potential (VEP) test showed marked delayed P 100 latency and reduced amplitude in the right eye. Left eye was unremarkable and VEP in the left eye was within normal limits. The child was pale, but there was no lymphadenopathy or hepatosplenomegaly or mucocutaneous bleeds.

Investigations revealed a hemoglobin of 8.5 gm/dL, total counts of 12.5×10^9/L (polymorphs: 67%, lymphocytes: 20%; and blasts: 11%), and platelets of 112×10^9/L. Peripheral smear showed microcytic hypochromic anemia, white blood cells were normal in number and morphology with occasional blasts and thrombocytopenia. Renal and liver parameters were normal. Tumor lysis workup was normal.

Magnetic resonance imaging of orbit revealed a large, lobulated homogenous lesion in the right orbit, involving the superior, lateral, and inferior extra- and intraconal space extending into the pterygopalatine fossa and the cheek causing medial globe displacement. Lateral rectus and inferior rectus could not be identified separately from the mass. The lesion displayed intermediate signal on T2-weighted imaging and was involving bilateral maxillary sinus causing bony erosion (►**Fig. 2**).

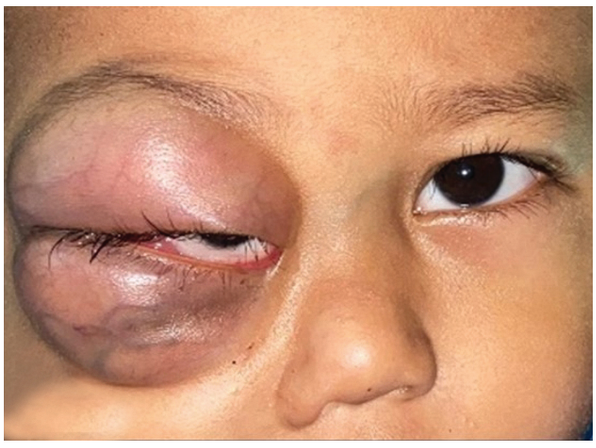

Fig. 1 Right eccentric proptosis and periocular fullness with engorged and prominent upper lid and lower lid vessels.

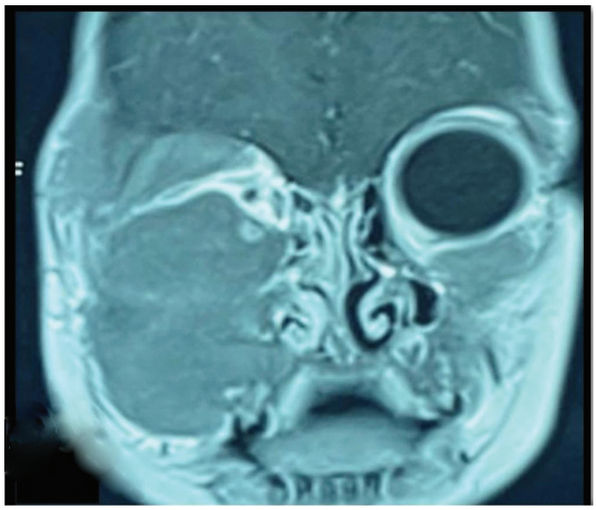

Fig. 2 Magnetic resonance imaging orbit plain, T2-weighted imaging coronal view depicting large, lobulated homogenous lesion in the right orbit, involving the superior, lateral, and inferior extra- and intraconal space extending into the pterygopalatine fossa and the cheek causing medial globe displacement. It is involving bilateral maxillary sinus causing bony erosion.

The child underwent an incisional biopsy of the lesion from the inferior quadrant via transconjunctival approach under general anesthesia. The rubbery, pink mass was composed of monotonous intermediate-sized round lymphoid cells with nuclear molding, prominent nucleoli, numerous mitoses with scattered tangible-body macrophages showing a starry-sky pattern. The neoplastic cells had molding with rounded and prominent nucleoli and numerous mitosis were seen.

IHC revealed CD20, CD10, CD5, CD3, Tdt, Bcl-6 negativity, and strongly positive for CD79a, Bcl-2, and C-MYC (> 95%) and Ki-67 index of more than 95%.

For metastatic evaluation of the disease, child underwent whole body positron emission tomography-computed tomography (PET-CT) and bone marrow aspiration and biopsy. PET-CT showed fluorodeoxyglucose (FDG) avid soft tissue mass (standardized uptake value [SUV]: 3.5) in bilateral orbital extraconal spaces, premaxillary, infratemporal fossa, and buccal spaces. There were permeative destruction of anterior end of bilateral zygomatic arch, lateral walls of bilateral maxillar sinuses, maxillary alveolus, and floor of orbit with aggressive sunburst type of periosteal reaction. FDG avid (SUV: 2.6) bilateral upper deep cervical lymph nodes of 7×17 mm were noted. An extra-axial soft tissue density enhancing lesion of size 18×11 mm was seen in the right frontal and interhemispheric falx. FDG avid epidural and paravertebral soft tissue lesions were seen in L4-S1 (30×10 mm; SUV: 2.4) and at S2-S4 levels (24×6 mm;

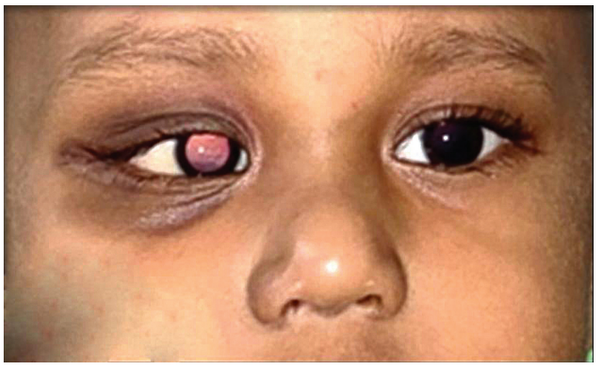

Fig. 3 Complete resolution of proptosis of right eye.

SUV: 2.1). Mild diffuse increased FDG uptake was noted in distal metadiaphysis of left femur.

Bone marrow aspirate showed reactive marrow and bone marrow biopsy showed reactive marrow with trilineage hematopoiesis. In view of double-expressor status, FISH for C-MYC, BCL-2, and BCL-6 translocations was done that was normal, ruling out DHL.

Child was finally staged as group C double-expressor high-grade B cell lymphoma and was started on LMB-96 protocol and received firs cycle of chemotherapy with vincristine, prednisolone, and cyclophosphamide. There was a significant reduction in the size of right eye lesion after 1 week of chemotherapy and child is currently well and on ongoing chemotherapy. At 3 months after diagnosis, the proptosis had reduced and patient had developed a left esotropia (►**Fig. 3**). Childs post-chemotherapy VEP showed improved P100 latency and amplitudes as well.

Discussion

In view of their unique biology and clinical behavior, World Health Organization in 2016 revised the classification for lymphoma and included a new category of lymphoma called high-grade B-cell lymphoma with translocations involving Myc gene and Bcl-2 or Bcl-6 genes or cases with blastoid morphology without translocations. Lymphomas expressing MYC, BCL-2, and/ or BCL-6 at IHC level with staining threshold more than or equal to 40% for MYC and 50% for BCL-2 but not related to chromosomal rearrangement are known as double-expressor or triple-expressor lymphomas.[2] Those tumors that harbor a rearrangement of MYC gene and the BCL-2 or BCL-6 are called DHL and if it involves all the three, is called triple hit lymphoma (THL).[3]

c-MYC is a transcription factor, involved in cell growth and proliferation. The gene located on chromosome 8q24, is strictly regulated, resulting in low c-MYC protein levels and induces apoptosis by increasing the expression of P53 under normal physiological conditions. But increased expression of BCL-2 or mutation of P53 enhances the oncogenic potential of MYC. The *c-myc* gene is an oncogene, and transforms cells via unregulated overexpression of intact c-MYC protein through gene mutations, amplifications, and chromosomal translocation.[4] The *c-myc* gene translocation with an immunoglobulin gene is characteristic of Burkitt lymphoma.

BCL-2 is an antiapoptotic gene and BCL-2 overexpression is synergistic with MYC, contributing to the chemoresistance and disease progression. BCL-6 is a proapoptotic gene and suppresses the activity of BCL-2 and MYC. The loss of the downregulatory effect due to mutations or translocations in BCL-6 causes lymphoma.[5] In the absence of chromosomal translocations, MYC and BCL-2 overexpression is attributed to gene amplification and posttranslational process.[6] The concurrent high expression of both MYC and BCL-2 is associated with high risk of treatment failure and the complex mechanisms of their individual contributions in terms of resistance are still unexplored.

As per Lunenburg biomarker consortium analysis, 53% of those with a MYC translocation had a rearrangement of BCL-2 and/or BCL-6 translocations, 60% of high grade B cell lymphoma had dual MYC and BCL-2 translocations, and 20% had MYC and BCL-6 translocations.[7] DEL accounts for 20 to 30% of DLBCL cases, whereas DHLs are present in approximately 10% of DLBCL cases.[2,8] Among DHLs, MYC/BCL-2 accounts for 65% and MYC/BCL-6 accounts for 14%.[9]

Activated B cell type is more common in DEL and germinal center B cell type is seen in DHL.[10] DHLs are reported to be extremely rare in younger children less than 18 years of age.[11] DHL and THL have a very poor prognosis due to their aggressive nature, advanced stage at presentation, and involvement of extranodal sites—bone marrow and CNS. An underlying indolent lymphoma can also transform into a DHL.[12] Our child too presented with extensive disease in terms of CNS involvement and extranodal location of primary tumor in the orbit.

Overexpression of MYC causing proliferative oncogenic signals and antiapoptotic survival advantage of BCL-2 overexpression results in poor outcomes with conventional chemotherapy.[13] DHLs have a 4 to 7% risk of CNS relapse or progression. Patients with DEL demonstrated a 10% risk of CNS relapse at 2 years.[14]

Unlike DH/TH lymphomas that harbor MYC and BCL-2 rearrangements, MYC and BCL-2 copy number variations do not have the high-risk gene expression. Hence, it is important to differentiate the DHLs from the larger group of DELs. DELs have better prognosis than double or THLs but have worse prognosis than the ones that does not express MYC or BCL-2 proteins. Green et al have demonstrated that patients with DEL had distinct clinical phenotype in terms of higher median age, advanced disease status with multiple extranodal sites, poor performance status, higher Ki-67 proliferative index, intermediate/high-risk International Prognostic Index (IPI) scores, and poor response to Rituximab -cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy.[15]

Double-expressor status is an adverse predictive factor and Hatzl et al have quoted a 5-year survival rate of 33% for DELs.[16] Relapse-free survival and overall survival (OS) improved with intensive induction regimens rather than with R-CHOP.[17]

No difference was reported in overall, event-free survival, and complete remission (CR) rates between dose adjusted

etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin -Rituximab (DA-EPOCH-R) and R-CHOP at a median follow-up of 5 years.[18]

In the multicenter, study of 311 patients with DHL, Petrich et al have reported that there was no OS benefit with transplant after achieving first induction remission.[19]

Wu et al have reported that lymphomas with translocations involving c-MYC and BCL-2 had common immunophenotype in terms of decreased CD20 expression ranging from dim to absent.[20] In our case, though the translocation for MYC, BCL-2, BCL-6 was negative, IHC was negative for CD19, CD20 as seen in DH lymphomas.

All the studies quoting DELs were adult studies and to the best of our knowledge, DEL has not been reported in children less than 3 years old. In the study by Hwang et al on 41 studies of 7054 patients for double-expressor status, the youngest child reported was of 7 years of age.[21]

While non-Hodgkin lymphoma (NHL) is rarely diagnosed before 5 years of age, Bharatnur et al have reported NHL in a 2-year-old child and Biswas et al had reported a primary ovarian NHL in a 1-year-old patient.[22,23] Primary NHL of the orbital region is rare, representing 1 to 2% of all NHL and 8 to 10% of all extranodal sites. Our case is unique in terms of age of presentation and extranodal site and double-expressor status. Though our child had significant clinical response to the initial cycles of treatment, long-term follow-up is needed to assess the overall survival rate.

Conclusion

FISH analysis for c-MYC, BCL-2, and/or BCL-6 is recommended in cases with aggressive clinical presentation, blastoid, or B cell lymphoma unclassified morphology, Germinal Center B cell (GCB) phenotype, and in cases with double expression of MYC and BCL-2 to identify the much severe DH or TH lymphoma subtypes. Novel large multicentric studies and rational targeted therapies are essential to treat this unique molecularly defined group that are very rare in pediatric age groups.

Authors' Contributions

Latha MS conceptualized the report, performed literature review, and edited the manuscript. Anjali Shaju and Nidarshana Pandian drafted the manuscript. Krishnakumar, Suresh Chandra, Priyathersini, and Sonam Poonam edited and revised the manuscript. All authors read and approved the manuscript for publication.

Patient's Consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

None declared.

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Primary Intracranial Extraskeletal Mesenchymal Chondrosarcoma of the Brain in a Pediatric Patient: A Case Report and Review of Literature

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Abstract

Intracranial extraskeletal mesenchymal chondrosarcoma, which is characterized by undifferentiated mesenchymal cells in the presence of occasional pockets of mature hyaline cartilage, is rare in our clinical practice and commonly seen in young adults. In the pediatric population, only a few cases have been reported. In this article, we describe a case of primary recurrent intracranial mesenchymal chondrosarcoma in an 11-year-old boy well treated by surgery, radiation, and chemotherapy. We also reviewed all previously published reports on pediatric patients on the basis of their manifestations and management.

Keywords

- reirradiation
- intracranial
- management
- mesenchymal chondrosarcoma
- outcome
- pediatric

Introduction

Dahlin and Henderson reported the first case of intracranial extraskeletal mesenchymal chondrosarcoma (IEMC) in 1962.[1] It accounts for less than 0.16% of all intracranial tumors and has origins in the basal synchondroses or different parts of the meninges along the different dural folds.[1] The most frequent sites of origin in the central nervous system are often the meninges of the brain and spinal cord. The ideal course of treatment for IEMC is unknown at the moment, and there is scant information in the published literature concerning the procedure. With our case and previous literature review, we want to enlighten the reader about the usual clinical presentation, natural course of disease, and definitive treatment protocol for these patients. In pediatric patients, this aggressive intracranial tumor should be considered a differential diagnosis.

Case Report

An 11-year-old boy was apparently well in 2015, when he developed headaches in the frontal region, nausea, vomiting, a projectile nature, and abnormal body movements of all four limbs. His parents also complained about him using inappropriate words and losing social inhibition. Other systemic examinations were unremarkable. A giant, heterogeneously hyperintense mass of $5.6 \times 5 \times 4.6$ cm occupied the left basifrontal region, extending into the suprasellar region, abutting the pituitary gland, involving the frontal lobe and frontal horn of the ventricle, and infiltrating the corpus callosum, inferiorly reaching up to the body of the sphenoid body, laterally into the parasellar region, and up to the medial temporal lobe. Its expansion caused a mass effect and a midline shift of up to 10 mm. The patient underwent frontal craniotomy, and subtotal resection (STR) of the tumor was done.

The mass, which was reddish-brown and firm in consistency, had a gritty sensation during surgery and was enucleated partially without any postoperative complications. A pathologic examination revealed the mesenchymal chondrosarcoma. Until September 2016, the patient received adjuvant radiotherapy (RT; 54Gy in 30 fractinations), followed by six cycles of adjuvant chemotherapy (vincristine,

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doxorubicin, and cyclophosphamide, or VAC). Following that, the patient was subjected to regular follow-up. In October 2021, there was a resurgence of the initial symptoms. The patient presented to the department of neurosurgery in the outside center with a complaint of multiple seizure episodes, progressive in intensity and frequency, not well controlled on antiepileptics, and associated with behavioral changes, but other neurological examination was within normal limits.

Magnetic resonance imaging (MRI) of the brain revealed regrowth of the previous tumor, a $3.9 \times 4 \times 4.1$ cm, well-defined round lesion in the left frontal lobe, extending to involve the left hypothalamus, basal ganglia, optic chiasma, and left optic nerve completely encased, and left superior temporal lobe. With tumor infiltration, the orbital fissure has widened at the orbital apex, and he was seen at our institution for a second opinion and further management. He underwent a second surgery and had the tumor subtotally resected. Histopathological examination of the specimen shows spindle-shaped cells without any cartilaginous tissue (hematoxylin and eosin, $10\times$ and $40\times$). Immunohistochemical studies showed positivity for S-100 (►**Fig. 1**) and vimentin (►**Fig. 2**), which were always present, focally positive for GFAP and negative for synaptophysin, neurofilament, cytokeratin, SMA, caldesmon, EMA, ERG, MUC4, and NeuN with ki67 of 1%.

The morphology and immunophenotype of the tumor were almost unchanged over the 6-year period. The absence of necrosis and decreased mitotic activity were noted in the second histopathological specimen. Postoperative MRI of the brain showed no evidence of residual disease. Previous histopathology was also reviewed. Both histologies showed a low-grade mesenchymal tumor with an area of necrosis. A chest computed tomography (CT) scan is suggestive of multiple lung metastases. For systemic control, we start the patient on a multiple receptor tyrosine kinase inhibitor, *pazopanib* 400 mg daily. Due to a symptomatic intracranial lesion, he was planned for reirradiation at the dose of 36 Gy in 20 fractions, to restrict the cumulative dose of the optic apparatus. The patient completed reirradiation with oral pazopanib 400 mg daily on June 20, 2022. After that, the patient is on regular monthly follow-up and oral pazopanib 600 mg daily. At present, he is doing well with good symptomatic improvement. His response assessment scan is planned for the last week of November 2022.

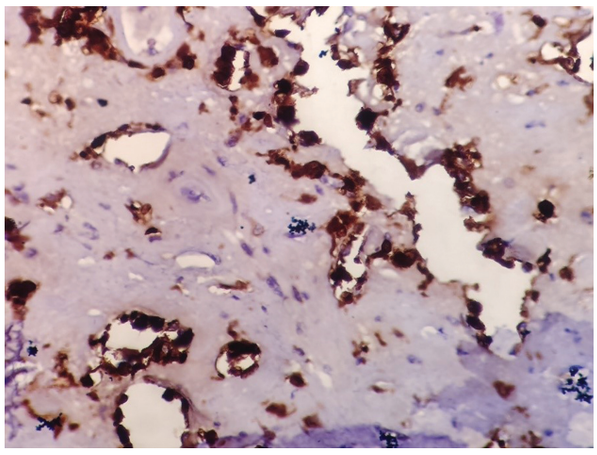

Fig. 1 Immunohistochemical examination shows diffuse positivity of marker S-100, which is always positive in intracranial chondrosarcoma.

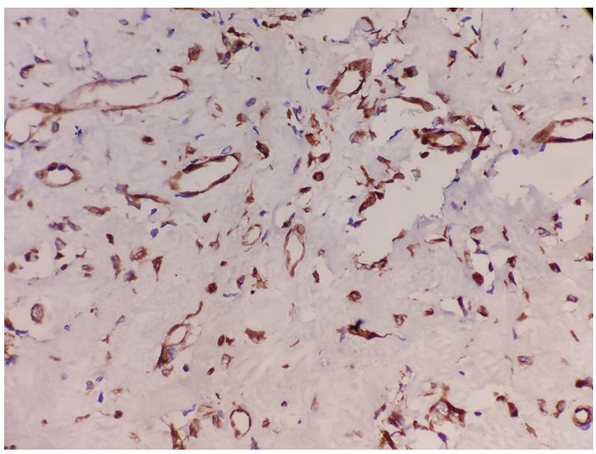

Fig. 2 Immunohistochemistry of highly cellular tumor showing positivity of vimentine.

Discussion

Background

The term "mesenchymal chondrosarcoma" was coined by Lightenstein and Bernstein in 1959 based on the histopathological findings they observed in a special type of unusual chondroid tumor that originated from bone. In 1962, Dahlin and Henderson reported an intracranial tumor in a 44-year-old female patient, which is known to be the first case of IEMC.[1,2] However, until now, most commonly reported tumors had an origin from the base of the skull, with very few reports of intracranial extraskeletal chondrosarcomas in pediatric patients.[3] Mesenchymal chondrosarcoma is a variable-grade malignant tumor of the brain with a high propensity for locoregional recurrence and occasional metastasis, commonly in adult patients. Only one case other than ours with distant metastasis was reported in previous literature about pediatric patients.

Radiological Findings

Following a clinical examination, radiological investigation, such as a CT scan, MRI, or angiography, is required to evaluate any vascular intracranial lesion. Because of the rarity of this tumor, other differential diagnoses should be ruled out radiologically before diagnosis and are also important for surgical decision-making by evaluating the possible neurovascular involvement and the extent and involvement of the mass in a diagnostic MRI. Dural base lesions such as meningioma or low-grade gliomas such as oligodendroglioma, astrocytoma, and hemangiopericytoma should be the preoperative differential diagnosis. Plain skull X-rays, though rarely utilized, show signs of raised intracranial pressure such as a "beaten copper" appearance, stippled calcification,

or destructive changes.[4] Because of its high vascularity, MRI is the imaging modality of choice for IEMC. A well-defined lobulated brain lesion with T1-contrast hyperintensity, isointensity, or homogenous hyperintensity of the T2-weighted image is the characteristic MRI finding in IEMC.[5]

Consequently, for the same reason, especially for larger lesions, angiography in the preoperative setting allows prophylactic embolization to reduce blood loss during resection. After the initial treatment, metastasis to extracranial sites was very rare in pediatric patients. A spinal metastasis was reported after a long dormant period, but our case had multiple lung metastases.[5–8] That is why, as metastatic work-up in the form of a CT scan of the thorax is mandatory in primary IEMC, and to rule out the primary from the other site, a whole-body positron emission tomography (PET)-CT scan or bone scan with contrast-enhanced CT of the thorax and abdomen should be considered mandatory investigations.

Tumor Characteristics and Presentation

The most common presentation of IEMC is due to raised intracranial pressure or direct compressive impact on surrounding structures. Intraoperative findings of these tumors are seen as smooth tumors, with a color ranging from grey to red, depending on the grade. During tumor resection, they are firm to hard to the touch with a gritty sensation.[6,9,10] The histological features are not consistent. IEMCs typically have the appearance of a small round cell cluster or sheet with or without hyaline cartilage islands.[9] Due to the absence of this characteristic cartilaginous part in histopathology, the diagnosis of IEMC has become very challenging. In a case like ours, where the typical histological pattern is absent, other common differential diagnoses should be ruled out first. In the pediatric age group, parenchymal lesions such as supratentorial primitive neuroectodermal tumor, high-grade non-Hodgkin's lymphoma, malignant hemangiopericytoma, or lesions originating from the base of the skull, such as chondrosarcoma at the skull base, embryonal rhabdomyosarcoma, or small cell osteosarcoma, should be the other differentials.[11–15] That is why, IHC is important to distinguish between those diagnoses, but no proper Immunohistochemistry (IHC) patterns have been identified till now, which is characteristic of IEMC. However, it is almost always positive for vimentin and S-100 and negative for synaptophysin, chromogranin, and EMA, but occasionally positive for GFAP (25% of the time).

Origin of the Tumor

Intracranial chondrosarcoma can be divided into classic, mesenchymal, and myxoid variants. The difference lies in the findings in histopathology, presentation, and outcome. Due to its rarity, the origin of intracranial mesenchymal chondrosarcoma is still not clear. In different studies, multiple hypotheses were proposed. The primary origin of the tumor is thought to be from either the meningeal layers or intraparenchymal. It can also be from the embryonic cartilaginous rest cells in the cranial bones and dura, as there were reported cases in pediatric patients, or premesenchymal chondroprogenitor cells, meningeal fibroblasts, or mesenchymal cells in the dura or arachnoid. Among them, dural-based lesions were more abundant (66%) than parenchymal (37%) lesions in the pediatric group of patients.[4,16] Previous reports have usually shown that dural-based lesions have better survival rates than parenchymal lesions. In this series, dural-based lesions had a mean overall survival of 53.8 months, compared with 28 months for parenchymal lesions, and there was a trend toward improved survival in patients with tumors having dural attachment.

Location

Eighty percent of these tumors are supratentorial in location, and the origin is dural-based. In our review, we found that this was also true for the pediatric group of patients. Almost 86% ($n = 18$) of the tumors are supratentorial in location, with the most common site being the frontal region. In our case, the tumor is supratentorial- and parenchymal-based. Chondrosarcomas that arise at the skull base should be differentiated from intracranial mesenchymal chondrosarcomas, as the origin of skull base tumors is cartilaginous synchondroses that are usually located in the parasellar region, the cerebellopontine angle, cavernous sinuses, larger skull foramens, and the petrous part of the thoracic bone region. In our series, very few reported cases ($n = 3$) have origins in other locations in the brain; thus, survival differences in different locations cannot be determined.

Role of Surgery

All the cases in the literature review have been treated primarily with surgery (►**Table 1**), including our reported case that underwent more than one resection despite lacking any consensus about the treatment strategy.[17,18] The majority of these tumors have been described as highly vascular lesions. Despite this, radical removal of these lesions is the mainstay of management, regardless of their anatomic location. When treated surgically, maximum safe resection is the goal. Gross total resection (GTR) is the most desirable for any intracranial tumor, and it is not different for IEMC. According to our review, 57% of patients had GTR and had a higher survival rate (mean overall survival = 49 months) than STR, which had a lower survival rate (mean overall survival = 39 months). This could be a poor prognostic factor that is related to an inability to get a GTR to prevent tumor spread and recurrence.[9,10,19]

Role of Radiotherapy

Adjuvant RT should be an appropriate therapeutic option as this is a locally aggressive tumor with a high rate of local recurrence. In the literature review, there was no overall survival difference between adjuvant RT and non-RT patients. However, there is a significant improvement in overall survival with adjuvant RT after STR (STR + adjuvant RT, $n = 5$, mean OS = 54.4 months vs STR without RT, $n = 4$, mean OS = 20 months). Thus, postoperative adjuvant RT is a preferred treatment for the tumor that could not be completely resected. Some authors also consider adjuvant RT if the diffuse or infiltrative nature of the tumor is described by the neurosurgeon even after GTR.[2] Also, other

Table 1 Previously published case with our case report of intracranial extraskeletal chondrosarcoma in pediatric population

Serial number	Study	Age	Sex	Size	Location	Attachment	Surgery	RT	Dose	CT	Drug	Follow-up	Recurrence	Metastasis	Location
1	Flyger et al 1963[17]	11 y	M	5 × 4 × 3	Frontal	Parenchymal	GTR	No		No		3	No	No	
2	Scheithauer et al 1978[9]	7 y	M		Parietotemporal	Dura	GTR	No		No		84	Yes	No	
3	Rollo et al 1979[7]	11 y	M		Parietal	Dura	STR	Yes	48 Gy	No		96	Yes	Yes	Spinal
4	Kobayashi et al 1980[20]	11 y	M		Parietal	Dura	GTR	No		No		216	Yes	No	
5	Rodda et al 1984[31]	12 y	F		Frontoparietal	Parenchymal	GTR	No		No		7	No	No	
6	Chhem et al 1992[21]	11 y	F	3.5 × 3.5	Parietal	Parenchymal	STR	Yes	60 Gy	No		18	No	No	
7	Schut et al 1994[22]	1 y	M		Frontal	Dura	STR	No		No		NK	Yes	No	
8	Schut et al 1994[22]	12 y	F		Frontal	Dura	STR	Yes	NK	Yes		NK	Yes	No	
9	Rushing et al 1996[19]	5 y	M		Frontal	Dura	GTR	Yes	44 Gy	No		14	No	No	
10	Rushing et al 1996[19]	7 y	F		Sphenoid	Dura	STR	No		No		60	No	No	
11	Rushing et al 1996[19]	11 y	F		Frontal	Dura	STR	Yes	55 Gy	No		20	No	No	
12	Malik et al 1996[23]	8 y	M		Cerebellum	Parenchymal	GTR	Yes	NK	Yes		NK	No	No	
13	Crosswell et al 2000[24]	6 mo	M	10 × 9 × 6	Frontoparietal	Dura	GTR	No		Yes	A + E + C	2	No	No	
14	Sardi et al	12 y	M		Frontal	Dura	GTR	No		No		NK	No	No	
15	Sardi et al[32]	12 y	F		Falcine	Dura	GTR	No		No		30	No	No	
16	Kan et al 2012[25]	11 y	F		Parietal	Parenchymal	GTR	Yes	NK	No		18	Yes	No	
17	Sadashiv et al[33]	7 y	M		Occipital	Parenchymal	STR	No		No		6	Yes	No	
18	Waliuddin et al 2006[26]	4 y	M	9 × 8 × 6	Temporoparietal	Dura	GTR	Yes	NK	No		4	Yes	No	
19	De Cecio et al 2008[11]	2 mo	M	11 × 9 × 6	Parietal	Dura	GTR	No		No		NK	No	No	
20	Fanburg-Smith et al 2010[27]	12 y	F		Frontal	Dura	STR	No		No		NK	No	No	
21	Our study	11 y	M	5.8 × 5 × 4.6	Frontal	Parenchymal	STR	Yes	56 Gy	Yes	V + A + C	84	Yes	Yes	Lung

Abbreviations: CT, chemotherapy; GTR, gross total resection; RT, radiotherapy; STR, subtotal resection; A, Adriamycin; E, Etoposide; C, Cyclophosphamide; V, Vincristine; NK, Not Known.

chondrosarcomas, even those that originated at the base of the skull, are treated with surgery followed by adjuvant RT with or without adjuvant chemotherapy.[5,28] In regard to unresectable IEMC and those with residual disease in previously published cases, the authors mentioned that RT with or without concurrent chemotherapy is the best treatment option for these patients. As a result, adjuvant RT should be considered in all patients and made mandatory in those with inadequate surgery.

Role of Chemotherapy

Mesenchymal chondrosarcoma of other sites is typically a high-grade tumor, and multiagent chemotherapy in the form of neoadjuvant and adjuvant therapy, as with Ewing's sarcoma, is the mainstay of treatment. The benefits of chemotherapy in intracranial mesenchymal chondrosarcoma are still unclear, as these tumors have no current reliable evidence for its effectiveness, and a very limited number of patients received chemotherapy in an adjuvant setting, which failed to show any survival benefit. Chemotherapy is being studied; more data are needed to prove any benefit, but chemotherapy has been recommended in previous published cases.[29,30] However, in a metastatic setting, chemotherapy should be a part of treatment. Nevertheless, as the mesenchymal chondrosarcoma of the extracranial region is treated as Ewing's sarcoma, multiagent chemotherapy (vincristine, cyclophosphamide, doxorubicin, actinomycin-D, ifosfamide, and etoposide in different combinations) can be considered in adjuvant settings as well, especially in high-grade tumors or tumors with incomplete surgical resection.

Survival and Prognostic Factors

If we consider all subsites in the body, mesenchymal chondrosarcoma has a 5- and 10-year survival rate of 55 and 27%.[9] In pediatric patients, the 2-year overall survival rate is 48% in our review. Our review's 5- and 10-year overall survival rates of 33 and 10%, respectively, are slightly lower than those of conventional mesenchymal chondrosarcoma, indicating the tumor's most malignant nature, which is locally aggressive with a high rate of recurrence.[6] After discussing all those mentioned factors, we propose that the underlying factors that influence the prognosis of the tumor and overall survival include grade, location (supratentorial or infratentorial), origin of the tumor (dural or parenchymal), type of surgical resection (GTR or STR), and use of postoperative adjuvant RT or chemotherapy.

Review of Previous Published Cases

From our data sources, 20 cases have been reported in the literature before our patient. The ages ranged from 2 months to 12 years, with 8.5 years being the average (median age: 11 years). In our discussion, we only restrict ourselves to previously published pediatric cases with an age group of 12 or less patients and their clinical and available management details. In the pediatric group of patients, there is a slight male preponderance with a male-to-female ratio of 1.6:1. The size of the tumor ranges from 3 to 11 cm at its largest diameter. We found the origin of the tumor was also divided on the basis of dural or parenchymal. In our case report, the patient had a tumor of parenchymal origin without any dural attachment. In previously reviewed studies, dural and parenchymal tumors had a ratio of 3:2 (dural: $n = 14$; parenchymal: $n = 7$). Among all the patients, more than half underwent GTR ($n = 12$, 57%) compared with STR ($n = 9$, 42%). Of the 21 ($n = 9$; 42% of total) patients that received RT postsurgery with a dose of 44 to 60 Gy, only 4 (19%) had chemotherapy as an adjuvant setting, and chemotherapy details for 1 patient are available. Nine patients had local recurrences at the same site of origin. Only one patient had a distant recurrence to the spinal cord and was treated with palliative RT. The median overall survival for the entire set of reported cases where follow-up was provided was 20 months. Patients with GTR had a slightly better median survival than patients with STR. Patients with or without a RT group have no difference in overall survival.

Conclusion

IEMC in the pediatric population is an extremely rare and variable-grade neoplasm with a very high tendency to local failure and distant metastasis. Due to the lack of specific radiological and histopathological findings, it is a challenge to differentiate it from other common tumors. The treatment options are GTR followed by close postoperative follow-up with or without adjuvant treatment, or STR with adjuvant RT with or without adjuvant chemotherapy. RT may be considered to reduce the risk of local recurrence, and chemotherapy may be useful for systemic control. As these tumors are highly aggressive with the potential for local and distant failure, the patient should be kept under regular follow-up.

Authors' Contributions

D.S.: design, manuscript preparation; S.G.: clinical studies, data analysis; R.R.: literature search; S.A.: diagnosis; D.M.J.: manuscript editing; M.G.: manuscript review. This manuscript has been read and approved by all the authors.

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Conflict of Interest

None declared.

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A Case Series of Gestational Choriocarcinoma with Review of Literature

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Abstract

Choriocarcinoma can be gestational and nongestational. Gestational choriocarcinoma is rare with an incidence of 9.2 in 40,000 pregnancies in Asian population. They can occur following molar, partial molar pregnancy, abortion, or delivery. It is detected by elevated levels of serum beta-human chorionic gonadotropin (beta-hCG) and by imaging modality. The need for histopathological diagnosis for choriocarcinoma is debatable. Six cases of choriocarcinoma are described with variable presentations and outcomes. Out of six cases, three were following vaginal delivery, two were after abortion, and one case was perimenopausal with antecedent pregnancy 10 years ago, unclear whether it was the cause for choriocarcinoma. Brain and lung metastasis were seen in three cases each; one case, which had metastasis to all organs, had worse prognosis and succumbed to the disease. All belonged to high-risk group according to International Federation of Gynaecology and Obstetrics score (8–13). The prognosis is usually very good, provided that prompt diagnosis and treatment are initiated early. Long-term follow-up with beta-hCG levels needs to be done to detect recurrence but it did not act like a prognostic indicator in our case series.

Keywords
- choriocarcinoma
- gestational trophoblastic neoplasia
- metastasis

Introduction

Choriocarcinoma is a subtype of gestational trophoblastic neoplasia (GTN), an extremely malignant tumor. GTN also includes invasive mole, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Choriocarcinoma and molar pregnancy arise from cytotrophoblasts and syncytiotrophoblasts, whereas PSTT and ETT arise from intermediate trophoblasts.[1] It produces human chorionic gonadotropin(hCG) and is highly vascular.[2] Gestational choriocarcinoma is a rare malignancy with an incidence of 9.2 in 40,000 pregnant women in southeast Asia.[3] GTN can be distinguished into nonmetastatic and metastatic. Lesions that are limited to the uterus are termed nonmetastatic GTN. Lesions outside the uterus that spread typically through hematogenous dissemination are termed metastatic GTN.[4] Most common site of metastasis is lung, followed by vagina, brain, liver, and intestines.[4] Early diagnosis of gestational choriocarcinoma is crucial as it is highly chemosensitive and has an excellent prognosis, even in advanced stages.[3] This case series demonstrates different scenarios of choriocarcinoma. Here, we would like to share six cases of choriocarcinoma in the last 5 years in our hospital (►**Table 1**).

Case 1

A, P1L1A2, 24-year-old lady who had delivered 2 months back visited general hospital with postpartum persistent

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Table 1 Clinical presentations of the cases

No.	Age (y)	Clinical presentation	Antecedent pregnancy	Interval (mons)	Beta-hCG (mIU/mL)	Sites of metastasis	FIGO score	Treatment	Outcome
1	24	Postpartum persistent vaginal bleeding, altered sensorium, slurred speech	Vaginal delivery	2	1,08,000	Brain	12	6 cycles of EMACO Brain radiation	In remission; no relapse
2	32	Generalized weakness	Missed abortion (HPR—NA)	2	34,900	All organ metastasis	12	Ongoing 1st cycle of EMACO	Died
3	31	Lower abdominal pain	Incomplete abortion (HPR—NA)	3	5,872	Brain, lungs	12	2 cycles of EMACO; developed respiratory complication; discontinued treatment	Lost to follow-up
4	28	Pain abdomen, irregular vaginal bleeding	Vaginal delivery	13	68,000	Nil	8	6 cycles of EMACO	In remission; no relapse
5	52	Pain abdomen, generalized weakness	Vaginal delivery	120	2,26,150	Nil	13	6 cycles of EMACO followed by TAH + BSO	In remission; no relapse
6	32	Pain abdomen, amenorrhea	Vaginal delivery	18	8,49,850	Lungs	12	Still under treatment. Received 2nd cycle of EMACO	–

Abbreviations: Beta-hCG, beta-human chorionic gonadotropin; EMACO, etoposide, methotrexate, actinomycin-D, cyclophosphamide, oncovin; FIGO, International Federation of Gynaecology and Obstetrics; HPR, histopathology report; NA, not available.

Fig. 1 Computed tomography brain showing an intraparenchymal lesion in left frontoparietal region.

vaginal bleeding, for which she underwent dilatation and curettage. Histopathology report (HPR) showed features of choriocarcinoma (>5cm tissue). Her first pregnancy was partial molar pregnancy and second pregnancy was a missed abortion; HPR was not available. She came to our center with complaints of altered sensorium and slurred speech. At the time of presentation, her Glasgow Coma Scale was 12/15. Computed tomography (CT) brain (►**Fig. 1**) showed an intraparenchymal hematoma with perilesional edema in left frontoparietal region causing cerebrovascular attack with right hemiparesis and aphasia and a 5 mm mid-line shift. Chest X-ray was normal, and beta-hCG levels were 1,08,000-mIU/mL. Neurosurgery did not recommend any need for surgical intervention immediately as there was no active bleeding noted in brain parenchymal tissue and they advised to start chemotherapy.

Her International Federation of Gynaecology and Obstetrics (FIGO) score was 12 (high risk: <40 years old [24 = 0]), index pregnancy (vaginal delivery = 2), time since delivery (2 months = 0), beta-hCG (1,08,000mIU/mL = 4), size of tumor (>5cm = 2), metastasis (brain = 4), number of metastasis (two = 1), and previous failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, oncovin (EMACO) followed by cranial radiation therapy of 20 fractions. Post-treatment beta-hCG dropped to 5.13mIU/mL. Presently she has minimal right upper limb weakness and is on follow-up for the last 4 years.

Case 2

A lady aged 32 years, P1L1A1, underwent suction and evacuation for missed abortion at outside hospital 2 months ago but HPR was not available. She came to our center with generalized weakness and bilateral lower limb pain. On evaluation, beta-hCG levels was 34,900 mIU/mL and contrast-enhanced computed tomography (CECT) abdomen

showed intrauterine mass of 4 × 4cm suggestive of gestational trophoblastic disease with hepatic, pancreatic, renal, adrenal, and bilateral lung lesions, suggestive of metastatic deposit. Magnetic resonance imaging (MRI) brain showed left parietal hemorrhagic dural metastasis.

Her FIGO score was 12 (high risk): less than 40 years old (32 = 0), index pregnancy (abortion = 1), time since abortion (2 months = 0), beta-hCG (34,900mIU/mL = 2), size of the tumor (4 cm = 1), metastasis (liver and brain = 4), number of metastasis (>8 = 4), and previously failed chemotherapy drugs (no = 0).

She was started on EMACO chemotherapy regimen. During first cycle chemotherapy patient desaturated and succumbed to the advanced disease.

Case 3

A 31-year-old lady, G3A2, had undergone suction evacuation for incomplete abortion 2 months ago outside hospital. HPR was not available. She came to our center with 2 months of amenorrhea, lower abdominal pain, and excessive vomiting. Her beta-hCG was 5,872mIU/mL. Ultrasound abdomen showed an enlarged uterus with a heterogenous mass (>5cm) lesion within the endometrial cavity, infiltrating the myometrium, suggestive of GTN. CECT chest was suggestive of lung metastasis. MRI head showed hemorrhagic vascular periventricular deposits in the right corona radiata involving the choroid plexus of the bilateral lateral ventricle, third and fourth ventricle (brain metastasis).

Her FIGO score was 12 (high risk): less than 40 years old (31 = 0), index pregnancy (abortion = 1), time since delivery (<4 months = 0), beta-hCG (5,872mIU/mL = 1), size of the tumor (5 cm = 2), metastasis (lungs and brain = 4), number of metastasis (>8 = 4), and previously failed chemotherapy drugs (no = 0).

She was planned for six cycles of EMACO regimen and cranial radiation. She received two cycles of chemotherapy; later she developed complaints of breathlessness, hypotension and was diagnosed to have pulmonary edema. The patient and family discontinued the treatment in view of financial constraints and were lost to follow-up.

Case 4

A multiparous (P5L5) lady of 28 years presented to a hospital outside with 2 months duration of pain abdomen and irregular heavy menstrual bleeding. All were normal vaginal deliveries; last childbirth was 1 year ago. After dilatation and curettage, medical management for abnormal uterine bleeding was tried, but her symptoms were not relieved. Finally, they did a total abdominal hysterectomy with bilateral salpingectomy in that hospital. HPR showed features of choriocarcinoma (<3 cm tissue). Serum beta-hCG was 68,000mIU/mL. She came to our center and we did CECT chest and MRI brain that showed no evidence of metastasis.

Her FIGO score was 8 (high risk): less than 40 years old (28 = 0), index pregnancy (term = 2), time since delivery (>12 months = 4), beta-hCG (68,000mIU/mL = 2), size of the tumor (<3 cm = 0), metastasis (no = 0), and previously failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with EMACO. Post-chemotherapy beta-hCG was 3.13mIU/mL. She is being followed up for the past 2 years and is doing fine.

Case 5

A 54-year-old perimenopausal woman, P6L6, presented to our hospital with lower abdominal pain. She had lost weight and experienced easy fatigability. Her last menstrual period was 6 months ago. Her previous cycles were normal. She had all vaginal deliveries, with no history of GTN and her last delivery was 10 years ago. On admission, she was pale and tachycardic, and systemic examination was normal. Uterine fundus was 12 weeks enlarged. Ultrasound abdomen revealed large hyperechoic heterogeneous lesion with cystic changes that measure 6.2 × 5.8cm, with no vascularity and no lesions in the liver and lungs. Beta-hCG was 2,26,150-mIU/mL. Chest X-ray and MRI brain were normal.

Her FIGO score was 13 (high risk): more than40 years old (52 = 1), index pregnancy (term = 2), time since delivery (10 years = 4), beta-hCG (2,26,150mIU/mL = 4), size of the tumor (>5 cm = 2), metastasis (no = 0), and previously failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with EMACO regimen. Beta-hCG levels dropped to 1.40 mIU/mL. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The patient is in good health and is being followed up in our center for the last 4 years.

Case 6

A, P2L2A1, 32-year-old lady presented with complaints of pain abdomen and amenorrhea for 2 months. Scan abdomen showed uterine mass and serum beta-hCG was 8,49,850-mIU/mL. She had delivered her second child 1½ years ago by normal vaginal delivery. Prior to this she had a molar pregnancy that was evacuated and followed by beta-hCG levels. MRI abdomen and pelvis (►**Fig. 2**) showed a well-defined multilobulated lesion measuring 10 × 10 × 12cms, arising from the fundus and posterior myometrium. CT chest showed multiple parenchymal lung nodular metastatic lesions. MRI brain was normal.

Her FIGO score was 12 (high risk): less than 40 years old (32 = 0), index pregnancy (term = 2), time since delivery (>12 months = 4), beta-hCG (8,49,850 mIU/mL = 4), size of the tumor (>5cm = 2), metastasis (lung = 0), and previously failed chemotherapy drugs (*n* = 0).

She is planned for six cycles of chemotherapy with EMACO. She has received two cycles of chemotherapy and currently under treatment.

Discussion

GTN is most commonly seen in reproductive age women. It is seen in 9.2 and 3.3 in 40,000 pregnant women in southeast Asia and Japan, respectively[3] and much rarer, that is 1 in

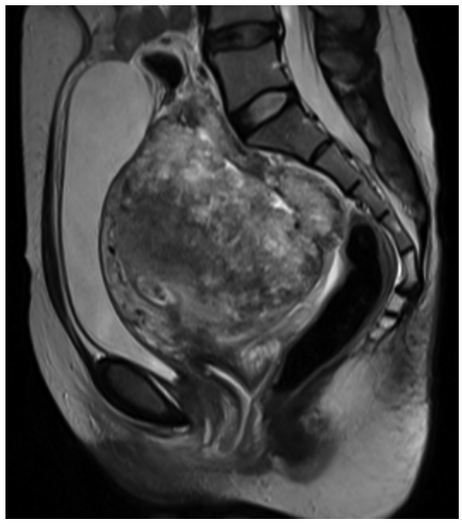

Fig. 2 Magnetic resonance imaging of pelvis showing multilobulated lesion of $10 \times 10 \times 12$cm arising from the fundus and posterior myometrium.

50,000 deliveries in United States of America.[2] It can occur after any antecedent pregnancy. It usually occurs 50% of cases after hydatidiform mole, 25% cases after spontaneous abortion, 22.5% after normal pregnancy, and 2.5% after ectopic gestation.[5] In our case series, out of six cases, three cases were after vaginal delivery that is difficult to diagnose as they present with abnormal uterine bleeding (either amenorrhea, irregular vaginal bleeding or persistent vaginal bleeding) and present to the hospital late. Two cases were after abortion where products were not sent for HPR, so it might have been a type of molar pregnancy that needed follow-up. It is extremely important to send the products for HPR. The case in perimenopausal age was nearly 10 years after her last pregnancy, so one cannot be sure what triggered the choriocarcinoma, whether it was the antecedent pregnancy or did it happen de novo. In such cases, it is difficult to say whether the antecedent pregnancy led to choriocarcinoma.[5]

Choriocarcinoma after nonmolar pregnancy is associated with worse outcomes due to delay in diagnosis and widespread metastatic disease, increased interval between onset of disease, and previous pregnancy.[6] In our case series, all were after nonmolar pregnancies and in that four had metastatic disease. So, high level of suspicion and prompt diagnosis and appropriate treatment with chemotherapy can save lives and will have very good prognosis. Choriocarcinoma can clinically present with abnormal uterine bleeding, acute pelvic pain, and metastatic symptoms such as chest pain, cough, hemoptysis, dyspnea, epigastric pain, neurological deficits secondary to brain hemorrhage. GTN is further classified into metastatic and nonmetastatic disease. Nonmetastatic disease occurs in 15% of cases and metastatic disease in 4% of cases after complete mole evacuation. Metastatic disease is more often seen after nonmolar gestation.[7] Metastasis is most commonly to lungs 60 to 75%, vagina 40 to 50%, brain and liver 15 to 20%, spleen, central nervous system and intestines 10%, very rarely manifests as cardiac metastasis. In 30% cases, by the time of final diagnosis, metastasis would have already occurred.[5] In our case series, brain metastasis was seen in three cases, lung metastasis was seen in three cases, one case had multiorgan metastasis that had worse prognosis and succumbed to the disease, and two cases had no metastasis.

Initial diagnosis is made based on clinical features, serum beta-hCG, and pelvic imaging such as ultrasound and MRI. Beta-hCG is an excellent marker for diagnosis. First line of imaging is color Doppler USG, used to look for uterine cavity and vascularity. Choriocarcinoma is characterized by myometrial and vascular invasion.[8] As diagnostic adjuvants, CT or MRI can be used to assess depth of myometrial invasion and extrauterine spread. Chest radiography, high-resolution CT chest, and MRI brain are used to stage the disease.[5] Diagnosis is confirmed after histopathological examination of endometrial curetting or the placenta. The true incidence of choriocarcinoma may be higher than the reported data, likely due to missed cases as half of the cases are asymptomatic and routine pathological examination of placenta is not performed.[8]

The World Health Organization (WHO) prognostic scoring system is used for plan of management. If it is low risk (score < 6), single agent chemotherapy is given. If it is a high risk (score > 7), multidrug chemotherapy with or without surgery/ radiation therapy is the line of management. Beta-hCG is an excellent surveillance marker for choriocarcinoma but is not a prognostic indicator as in our series we found patients with low beta-hCG performed poorly. Five-year survival rate can be up to 90%.[2] GTN is a rare human tumor that can be cured even in the presence of widespread dissemination.[7] In all our cases, FIGO score ranged from 8 to 13, belonged to high-risk group. EMACO was the first line of choice for multidrug chemotherapy in our cases. One patient died and one lost to follow-up, one patient is currently under treatment, and other cases are under remission. Our patients who completed the treatment achieved undetectable beta-hCG levels after four cycles and went on to receive two more cycles of consolidation chemotherapy. The need for increased methotrexate dose was not required in our case 1 who had brain metastasis as she responded well to regular EMACO regimen and she also received brain radiation. In patients with brain metastases, an increase in the methotrexate infusion to $1g/m^2$ will help the drug cross the blood–brain barrier better and is found to be beneficial. Some centers also use intrathecal methotrexate of 12.5 mg.[9] This can be given at the time of CO when EMACO is used, or with the EP in the etoposide, methotrexate, actinomycin-D, etoposide, cisplatin (EMA/ EP) regimen. Some may give whole brain radiotherapy 3000 cGy in 200cGy daily fractions concurrent with chemotherapy or use stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy.[9]

Recurrence rate of conventional low-risk GTN is 1.6 to 3.1% and high-risk is 6.9%.[4] Even in cases of recurrence, a

good cure rate has been observed with the use of etoposide and platinum drugs, combined with surgical excision of drug-resistant lesions and radiation therapy. For patients failing to respond to regular EMACO regimen, multiple salvage therapies are also available. Other chemotherapy regimens include TP/TE (paclitaxel and cisplatin interchanged with paclitaxel and etoposide weekly), BEP (bleomycin, etoposide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), and ICE (ifosfamide, carboplatin, etoposide). Role of peripheral blood stem cell support and high-dose chemotherapy is uncertain. Role of immunotherapy in the management needs further investigation. The fact that GTN strongly expresses Programmed Death - Ligand 1 (PD-L1) has led to checkpoint inhibitor use in GTN, a significant advance of immunotherapy in recent years. Pembrolizumab (anti-PD-L1) has effectively induced complete responses in 75 to 80% of unresectable, chemo-resistant GTN, including cases that had failed high dose chemotherapy.[4]

In a case series of six cases, patients displayed a variety of unusual clinical manifestation including suspected pulmonary tuberculosis, lung mass, pneumonia, heavy vaginal bleeding, pelvic mass, and peritonitis that highlighted the importance of having a high degree of clinical suspicion of choriocarcinoma in women of reproductive age.[10] All their cases were with scores of 8 to 12, EMACO therapy and selective hysterectomy proved to be beneficial. Administering three cycles of consolidation chemotherapy after remission that is given every 15 days was their standard practice.

In a systematic review,[11] a total of 121 case reports pertaining to unusual clinical manifestations of gestational choriocarcinoma were analyzed. The age of patients reported ranged from 17 to 67 years, and the time period between the index pregnancy and development of choriocarcinoma varied from 4 weeks to as long as 25 years. This shows choriocarcinoma can occur in any age (even menopause) and several years after the antecedent pregnancy just like in our case 5 where diagnosing the disease becomes challenging. Cardiopulmonary complaints (20.66%) followed by gastrointestinal (18.43%) and central nervous system manifestations (17.67%) were found to be the most common.[11]

Though hematogenous metastasis is well known in choriocarcinoma that spreads to lung initially and liver is the most common organ to metastasize in the abdomen, authors noted intestine metastasis in 5% cases in their case series.[12] They recommended a comprehensive evaluation including whole abdomen CT for all patients, not only those with pulmonary metastases. Intestinal metastasis has a poor prognosis.

For those patients with widespread metastasis, starting with standard chemotherapy may cause sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure, any or all of which can result in early death that may have been the reason in our case 2 as she had extensive metastasis and succumbed to the disease during first cycle of EMACO regimen. To avoid this, the use of initial gentle rather than full-dose chemotherapy has been suggested. Induction with etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2, repeated weekly for 1 to 3 weeks, before starting normal chemotherapy appears to have eliminated early deaths in one series[13] and similar promising results were reported by others too.[14]

Conclusion

Obstetricians and clinicians should have increased awareness of varied symptoms and presentations; a choriocarcinoma can present with and importance of early diagnosis. Delaying in diagnosis results in poor prognosis. So, high level suspicion and prompt diagnosis and treatment with chemotherapy can save lives. Serum beta-hCG is an excellent surveillance marker for choriocarcinoma and can be monitored to detect recurrence but prognosis does not depend on the levels.

Authors' Contributions

All authors have agreed for the manuscript description. AT contributed to data collection and manuscript preparation. VS contributed to concept design and clinical treatment. NN contributed to manuscript preparation and editing.

Patient's Consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

None declared.

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Determining the Trend of Public Interest in Pediatric Solid Tumors: A Pre- and Post-COVID Pandemic Analysis

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The coronavirus pandemic has had a significant impact on our daily life and led to a surge in digitization and utilization of resources available on the Internet.[1] This shifting trend is also reflected in health care and medicine, where apart from general medical anxiety due to the pandemic, the public relied on information technology for addressing their medical concerns. Pediatric solid tumors often cause a degree of anxiety and stress among parents of the affected children.[2] With growing access to the Internet, parents of children diagnosed with cancer often resort to using its resources for finding further information related to their child's diagnosis and prognosis. We sought to evaluate the pre- and postpandemic interest in the information on pediatric solid tumors available on the Internet by the public.

Google Trends is a powerful, freely accessible tool that provides information on Internet search data and gives access to a largely unfiltered sample of actual search requests made to Google.[3] Google Trends was used to conduct search for terms from the parents' perspective after a diagnosis of an extracranial pediatric solid tumor for their child. Three common tumors used were "Wilms Tumor," "Neuroblastoma," and "Hepatoblastoma." The search terms list consisted of "Wilms Tumor," "Wilms Tumor Survival Rate," "Wilms Tumor Symptoms," "Wilms Tumor Treatment," "Neuroblastoma," "Neuroblastoma Survival Rate," "Neuroblastoma Symptoms," "Neuroblastoma Treatment," "Hepatoblastoma," "Hepatoblastoma Survival Rate," "Hepatoblastoma Symptoms," and "Hepatoblastoma Treatment." Searches were conducted for the "worldwide" trend between May 14, 2017 and January 15, 2023. Pre-coronavirus disease 2019 (COVID-19) was designated as May 14, 2017 to March 15, 2020, and post-COVID-19 was designated as March 15, 2020 to January 15, 2023. March 2020 was chosen as the designated midpoint because this was the month that World Health Organization declared COVID-19 a pandemic, stay-at-home orders were issued in most parts of the world, and elective surgeries were postponed.[4] The first 17 months were designated as the "immediate" postpandemic phase as it included the period of the first and second COVID-19 wave, and the next 17 months were designated as the delayed postpandemic phase. The data was collected from Google Trends in a monthly format as a search volume index (SVI). SVI is a weighted scale from 0 to 100 of searches for specific terms relative to overall search volume, which is calculated first using daily search interest and then normalized to control for the overall increase in the number of Internet searches over time. The search interest is then indexed to values ranging from 0 to 100 on a relative scale,[5] which allows us to gauge relative changes in search interest over that period. The monthly SVIs for all 12 search terms from May 14, 2017 to January 15, 2023 were compiled and evaluated by statistical methods (Mann–Whitney *U* test).

We noted a variability in the median SVI for the three solid tumor search terms. The search term "Wilms Tumor symptoms" had a significantly increased SVI in the immediate postpandemic phase (p 0.004) which persisted even in the delayed postpandemic phase (p 0.0002). The term "Neuroblastoma symptoms" did not show any change in the immediate postpandemic phase but had a significantly increased SVI in the delayed postpandemic phase. On the contrary, the term "Neuroblastoma" showed a decline in the entire postpandemic phase, and "Neuroblastoma treatment" showed a decline in the immediate postpandemic phase. No other terms showed any changes in their SVI. Neuroblastoma is the most common extracranial solid tumor of childhood, and

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with a decrease in access to the hospital and more teleconsultations during the pandemic,[6] there was a decrease in diagnosis. This might explain the reduced search volumes of an otherwise relatively common pediatric tumor.

The public interest in the symptomatology of Wilms Tumor and Neuroblastoma had increased in the postpandemic period, possibly because of increased medical anxiety and utilization of the Internet sources for allied differential diagnosis of abdominal distention and lump, while having limited access to a health care professional to examine the child.[7] The increased search attempts on Google might also reflect the possibility of increased detection of these diseases as the health facilities gradually lifted the COVID restrictions. The backlog related to health services that were previously stalled also would have led to an unprecedented increased diagnosis during the postpandemic period. Hepatoblastoma being an otherwise less common tumor, compared with the other two tumors, did not show an increase or decrease in the searches. Overall, the median SVI pre- and postpandemic did not show a significant difference for pediatric cancers. Future data and studies can possibly demonstrate whether this reflects a decrease in early diagnosis, which may cause worse outcomes in the affected children, or is due to the general underutilization of Internet-based resources by parents of these children.

Conflict of Interest
None declared.

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*Unresectable Stage-III NSCLC post CRT **In 1st line Extensive stage SCLC in combination with CT

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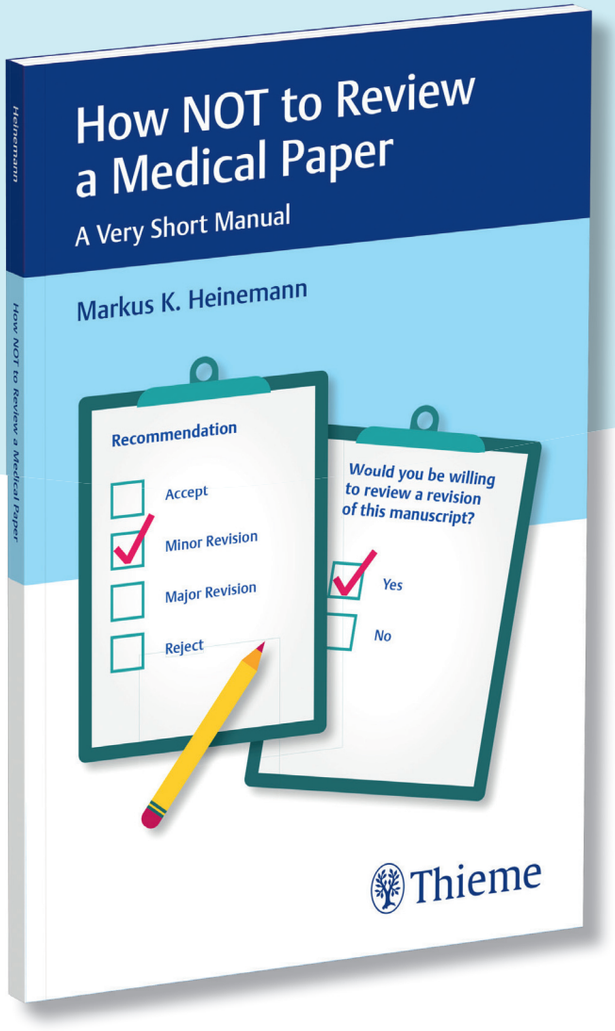

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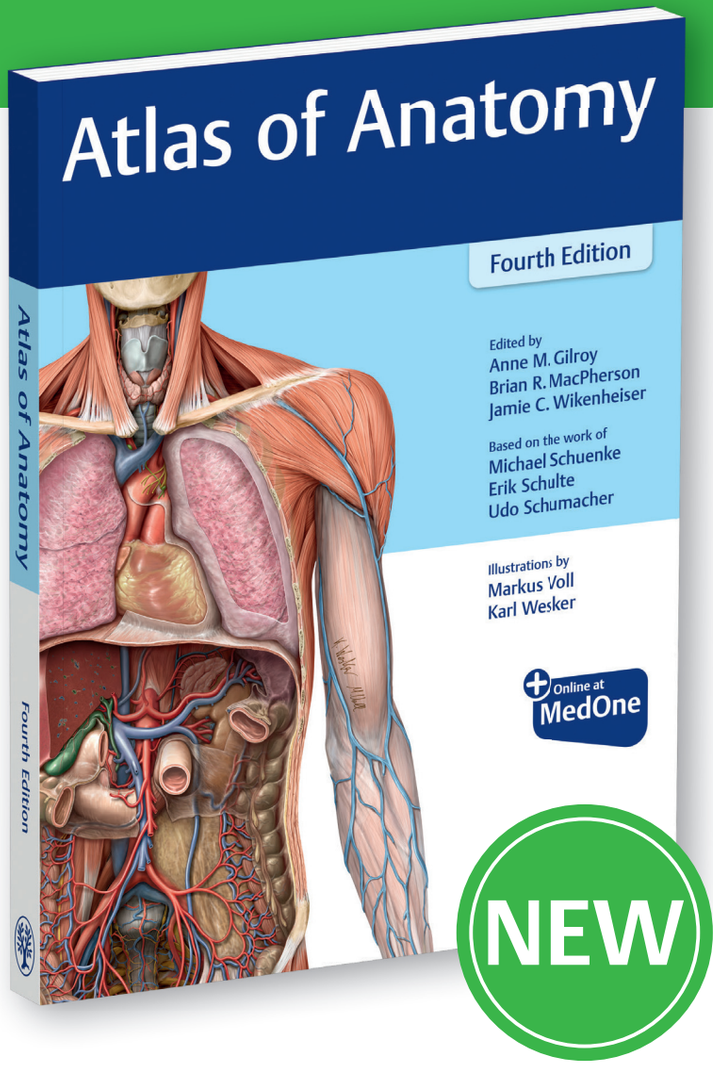

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