Article published online: 2024-12-13

Outcomes with Methotrexate-Free Dyad Chemotherapy in Osteosarcoma Patients: Audit from a Resource-Limited Setting

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Ind J Med Paediatr Oncol

Abstract

Objective To determine the disease free and overall survival of osteosarcoma patients and to evaluate the prognostic factors affecting OS for patients with localized disease.

Introduction Multiagent chemotherapy forms the backbone for the management of osteosarcoma. The globally accepted chemotherapy regimens for osteosarcoma include a combination of Adriamycin, cisplatin, and high-dose methotrexate (HDMTX). However, non-HDMTX regimens are predominantly used in India, secondary to patient profile, toxicity, administration, logistics, and financial constraints. We present our outcomes with a two-drug dyad chemotherapy consisting of Adriamycin and cisplatin in a resource-limited setting.

Material and Methods The study was a record-based analysis of all osteosarcoma patients presenting at a tertiary care referral center during the period from 2010 to 2019. A total of 127 patients of osteosarcoma were identified, who were evaluated for their demographic and clinical profile, while treatment details and outcomes were evaluated in 123 patients as disease-free survival (DFS) and overall survival (OS). Univariate and multivariate analysis was done for factors influencing OS.

Results The median age at presentation was 18 years and extremities were the most common site of presentation. Localized disease (LD) was seen in 102 (80%) patients, while 25 (20%) patients had metastatic disease (MD). Overall, 83 (84%) patients with LD underwent surgery, of whom 65 (78%) underwent limb salvage surgery, while 18 (22%) underwent amputation. Only 72 (73%) patients completed the planned six cycles of chemotherapy. At a median follow-up of 50.4 (range: 1–166.3) months, the 5-year OS for patients with LD and the entire cohort was 53 and 43%, respectively. For patients with MD, the 1- and 2-year OS were 41 and 7%, respectively. The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. Primary tumor measuring less than 12 cm ($p = 0.03$) and patients undergoing surgery ($p = 0.003$) were found to be statistically significant for improved OS on univariate analysis but not on multivariate analysis.

Keywords
- osteosarcoma
- pediatric tumor
- resource-limited setting
- chemotherapy
- non-high-dose methotrexate
- survival

DOI https://doi.org/10.1055/s-0044-1795133.
ISSN 0971-5851.

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

Conclusion The two-drug dyad chemotherapy was well tolerated with manageable toxicity. The outcomes were comparable with Indian studies using non-HDMTX regimens that report a 5-year survival of within 50 to 60%, but were inferior to global outcomes and the dose-dense OGS-12 protocol used in India. Raising awareness for early diagnosis, improving the nutritional status, incorporation of sequential third drug (ifosfamide), use of dose-intensive regimens for selected patients, and increasing compliance to treatment may further help improve the outcomes.

Introduction

Osteosarcoma is a rare bone tumor with an annual incidence of 0.3 per 100,000.[1] Nevertheless, in spite of its rarity, it is the most common primary bone tumor.[1,2] Osteosarcoma mainly affects children and adolescents.[2,3] The majority of osteosarcomas arise in extremities, and the lung is the most common site of metastases, followed by bones.[1,4]

Magnetic resonance imaging (MRI) is considered the investigation of choice for evaluation of primary bone tumor. Computed tomography (CT) scans of the chest and bone are preferred to exclude metastatic disease (MD).[2,4] Standard treatment for osteosarcoma consists of induction chemotherapy, followed by surgery and subsequent completion of adjuvant chemotherapy. Radiotherapy has limited role in view of relative radioresistant nature of the tumor.[4,5]

In developed countries, the overall survival (OS) for patients with localized disease (LD) and MD is around 60 to 75% and 30 to 40%, respectively.[6,7] Standard chemotherapy regimens in osteosarcoma include a dyad of chemotherapy consisting of cisplatin and doxorubicin or the MAP regimen: doxorubicin/cisplatin/high-dose methotrexate (HDMTX).[4–6] While HDMTX is the standard of care for the European and American patients, non-HDMTX regimens are predominantly used in developing countries. The hesitancy to use HDMTX regimens in developing countries is because patients present with poor performance status, costs, and excess toxicity. These patients undergo treatment in medical institutions with limited infrastructure in terms of indoor capacity. They also need constant drug-level monitoring and supportive care.[8,9] Non-HDMTX-based regimens are the most commonly used regimens in the majority of the cancer centers in India for high-grade osteosarcoma.[3,10,11]

Published data on osteosarcoma from India are very limited; hence, the exact magnitude and disease trend are not properly understood. There have been a few Indian studies in recent years, which report the 5-year survival rates as somewhat inferior to the world literature.[2,10,11] We present here the clinicodemographic profile, treatment patterns, and outcomes in terms of DFS and OS for osteosarcoma patients managed with dyad chemotherapy with Adriamycin and cisplatin (AC) in a resource-limited setting where patients generally present late with large tumors and poor performance status.

Materials and Methods

Study Design

This is a retrospective observational study that involves a record-based analysis of all osteosarcoma patients diagnosed and treated at a tertiary care referral center during the period from 2010 to 2019.

Sample Size

A total of 127 histopathologically proven patients of osteosarcoma were identified, who were evaluated for their demographic and clinical profile. One hundred and twenty-three patients who reported for treatment were evaluated for treatment details, recurrence patterns, and survival outcomes.

Inclusion and Exclusion Criteria

All biopsy-proven patients of osteosarcoma who underwent treatment at the tertiary care referral center during the period from 2010 to 2019 were included in the analysis. Patients who did not have a histopathology confirmation from the institutional pathology department or who did not receive treatment at our center were excluded from the analysis.

Primary and Secondary Outcomes

Primary outcomes included the following:

- Evaluation of the disease-free survival (DFS) and OS.
- Evaluation of the demographic and clinical profile of the osteosarcoma patients.

Secondary outcomes included evaluation of the prognostic factors affecting OS for patients with LD.

Study Setting

Data were analyzed for the demographic profile including age at presentation, gender, baseline body mass index (BMI) and hemoglobin levels, rural or urban residence, and any preexisting morbidities or addiction. The clinical profile was evaluated for symptoms at presentation, duration of symptoms before initiating treatment, tumor site, laterality, radiological investigation done for the primary site and MD, maximum size of the primary tumor, and the presence of LD or MD.

Treatment for LD or for patients with curative intent consisted of delivering three to four cycles of neoadjuvant chemotherapy (NACT) followed by surgery, which was followed by

adjuvant consolidation chemotherapy. As per our institutional protocol, three to four cycles of dyad chemotherapy were delivered in the neoadjuvant setting consisting of AC regimen[4] as follows.

Doxorubicin 25 mg/m^2/d IV over 2 hours (days 1–3), cisplatin 100 mg/m^2 IV over 3 hours (day 1), and cycles repeated every 3 weeks. Prophylactic growth factors were not used. The details of NACT and adjuvant chemotherapy delivered in terms of regimen, the number of cycles, toxicity, and timing with respect to local treatment were analyzed. Adjuvant radiotherapy was added for selected patients, predominantly for positive margins. Surgery and radiation details were also evaluated.

Response to NACT was assessed clinically and radiologically and decisions for surgery were taken. Histological evaluation for response to chemotherapy and extent of tumor necrosis was assessed using the Huvos grading system.[12] In the initial years when the Huvos grading was not done universally, many patients did not have the information available in the histopathology reports. Adjuvant chemotherapy was given with the aim to complete a total of six cycles.[4]

Management including chemotherapy protocols for patients with recurrent or MD were selected from the recommended options from standard treatment guidelines.[4] These protocols were individualized based on disease burden, site of metastases, general condition of the patient, and family decision. Recurrence patterns, treatment for recurrence, and MD were also analyzed. Outcomes were evaluated in terms of DFS and OS. OS was calculated from the date of registration in the department to death from any cause, while DFS was calculated from the date of registration to the first event (local recurrence, metastases, or death from any cause). Prognostic factors affecting OS for patients with LD were assessed.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences version 17 (IBM Inc., Chicago, IL, United States). Descriptive statistics were used for demographic and clinical parameters and treatment modalities, and were reported as median and percentages. OS and progression-free survival were estimated according to the Kaplan–Meier method, stratified by the LD and MD. Univariate and multivariate (Cox proportional hazards regression model) analyses were used to assess the factors influencing OS in patients with LD. Multivariate analysis was performed on the factors that were found to be significant on univariate analysis. A p value of less than 0.05 was considered significant. Age of patient (>21 years), gender, duration of presenting symptoms (>6 months), primary site (lower extremity vs. upper extremity), primary tumor size (<12 cm), number of chemotherapy cycles (≥6), use of surgery as local treatment, and grade of necrosis on histopathology were included as covariates on univariate and multivariate analysis.

Results

A total of 127 patients were evaluated for demographic and clinical profile. Four patients did not report for treatment. The remaining 123 patients were evaluated for treatment details, recurrence pattern, and outcomes.

Demography

In our registry, the median age at presentation was 18 years. The majority of patients had poor nutritional status as reflected by the BMI and baseline hemoglobin. Seventy-seven (61%) patients had a BMI less than 18.5 and 25 (20%) patients had baseline hemoglobin less than 10 g/dL. Details of age and gender distribution, BMI, residence, marital status, comorbidities, and addiction habits are listed in ►**Table 1**.

Clinicopathological Profile

Fifty-three (42%) patients presented 3 months after the onset of symptoms and 89 (70%) patients had a primary tumor greater than 8 cm at presentation. The majority of tumors,

Table 1 Demographic profile of osteosarcoma patients

Parameter	$n = 127$ (%)
Age (y)	
0–10	4 (3.2)
11–20	83 (65.4)
21–30	27 (21.3)
>30	13 (10.2)
Median age (y)	18 (8–63)
Sex	
Male	86 (67.7)
Female	41 (32.3)
Median hemoglobin (g/dL), *n* (range)	11.8 (6.8–15.6)
Median body mass index (BMI)	17.3 (4.8–31.8)
<18.5	77 (60.6)
18.6–22.9	39 (30.7)
>23	11 (8.7)
Residence	
Urban	44 (34.6)
Rural	83 (65.4)
Marital status	
Single	110 (86.6)
Married	17(13.4)
Morbidity	
Epilepsy	4(3.2)
Tuberculosis	4 (3.2)
CAD	2(1.6)
None	119 (93.7)
Addiction	
Tobacco	6 (4.7)
Alcohol	4 (3.2)
None	119 (93.7)

Abbreviation: CAD, coronary artery disease.

113 (89%), arose from the metaphysis. Conventional radiographs were done for all patients at presentation. The most common positive immunohistochemistry markers were SATB2, vimentin, and cytokeratin. Conventional osteosarcoma was the most common histology, followed by chondroblastic osteosarcoma. Details of presenting symptoms, site of presentation, and radiological investigations are listed in ►**Table 2**.

Systemic Treatment

Eighty-nine (89/99; 90%) patients with LD received NACT with a median of three cycles, while the remaining underwent upfront surgery. In the neoadjuvant setting, all patients received the AC regimen. Local therapy was followed by adjuvant chemotherapy with the aim to complete a total of six cycles; however, only 72/99 (73%) patients with LD completed six cycles of chemotherapy. In the adjuvant setting, 65/76 (86%) patients received the AC regimen, while 11/76 (14%) received the ifosfamide/etoposide (IE) regimen (►**Table 3**). During or within 4 weeks after completing adjuvant chemotherapy, 10 (10%) patients already had progressive disease.

Local Treatment

Overall, 83 (84%) of the 99 patients with LD underwent surgery, of whom 65 (78%) underwent limb salvage surgery, while 18 (22%) underwent amputation. Four patients with positive margins received adjuvant radiation after surgery with doses varying from 45 to 54 Gy. The degree of necrosis was assessed by Huvos grade on postoperative specimen. Of the 51 (57%) patients reported, only 12 (24%) patients showed grade 4 necrosis following NACT. Hematological toxicity was the predominant toxicity reported in these patients. The details are presented in ►**Table 3**.

Treatment for Relapse, Progressive, or Metastatic Disease

The most common sites of recurrence and metastases at presentation were the lungs seen in 31/39 (80%) and 24/24 (100%) patients, respectively. This was followed by bones. Chemotherapy was the predominant treatment modality with surgery and radiotherapy received by selected patients. The details of this treatment are reported in ►**Table 4**.

Outcomes

The median follow-up was 50.4 (range: 1–166.3) months. The 5-year OS for patients with LD and the entire cohort was 53 and 43%, respectively, while the 3-year OS for patients with LD and the entire cohort was 63 and 51%, respectively. For patients with MD, the 1- and 2-year OS was 41 and 7%, respectively (►**Fig. 1**). The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. A primary tumor size of less than 12 cm ($p = 0.03$) and patients undergoing surgery ($p = 0.003$), as compared with patients not undergoing surgery, were found to be statistically significant for improved OS on univariate but not on multivariate analysis in patients with LD. The details of univariate and multivariate analyses are reported in ►**Table 5**.

Table 2 Clinicopathological profile of OS of patients at presentation

Parameter	$n = 127$ (%)
Presenting symptom	
Pain	71 (56)
Swelling	94 (74)
Restricted movement	28 (22)
History of trauma	14 (11)
Pathological fracture at presentation	9 (7.1)
Duration of symptoms before reporting (mo)	
<3	74 (58.3)
3–6	30 (23.6)
6–12	15(11.8)
>12	8(6.3)
Site	
Extremity	122 (96)
Pelvis	2 (1.6)
Face (mandible)	1 (0.8)
Soft tissue/extraskeletal	2 (1.6)
Common extremity subsite	
Femur	59 (46.5)
Tibia	39 (30.7)
Humerus	19 (15)
Fibula	4 (3.2)
Laterality	
Left	72 (56.7)
Right	55 (43.3)
Radiological investigation for primary	
MRI	117 (92.1)
CT scan	10 (7.9)
Radiological size of primary	
<8 cm	38 (30)
8–12 cm	54 (42.5)
>12 cm	35 (27.6)
Radiology consistent with OS	64 (50.4)
Radiological investigation for metastatic disease	
CXR	9 (7)
CT chest	112 (88.2)
PET scan	6 (4.7)
Disease at presentation	
Localized	102 (80.3)
Metastatic	25 (19.7)
Bone marrow positive	10/38 (7.9)

Abbreviations: CT, computed tomography; CXR, chest X-ray; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography.

Table 3 Treatment for localized disease ($n = 99$)

Parameter	*n* (%)
Neoadjuvant chemotherapy	**89 (89.9)**
Median number of cycles	3 (1–6)
AC	89 (100)
Surgery	**83 (83.8)**
Limb salvage surgery	65 (78)
Amputation	18 (22)
Margin positive	4 (4.8)
Adjuvant radiotherapy	**4**
Dose: 45–54 Gy	4
Tumor necrosis	**51**
Grade 1	14 (27.5)
Grade 2	9 (17.6)
Grade 3	8 (15.7)
Grade 4	12 (23.5)
Adjuvant chemotherapy	**76 (76.8)**
Median number of cycles	3 (0–6)
Adriamycin/cisplatin	65 (85.5)
Ifosfamide/etoposide	11 (14.5)
Chemotherapy completed: 6 cycles	
Yes	72 (72.7)
No	27 (27.3)
Toxicity grade 3/4	
Anemia	18 (18.1)
Neutropenia	26 (26.3)
sepsis and shock	2 (2)
Vomiting	4 (4)
Renal failure	1 (1)
PD on 4 wk after adjuvant chemotherapy	10 (10.1)

Abbreviation: AC, Adriamycin and cisplatin; PD, progressive disease.

Table 4 Treatment for relapse/progressive/metastatic disease

Parameter	*n* (%)
Treatment for relapse/progressive disease ($n = 39$)	
Site of recurrence/progression	
Bone	8 (20.5)
Lungs	22 (56.4)
Lungs and bones	6 (15.4)
Lungs and brain	3 (7.7)
Local site	11 (28.2)
Treatment	
Chemotherapy	**28 (71.8)**
Median number of cycles	1 (1–6)
Gemcitabine/docetaxel	3
Adriamycin/cisplatin	3
Ifosfamide/etoposide	15
Gemcitabine/cisplatin	3
Gemcitabine	2
Oral metronomic	2
Surgery	**4 (10.3)**
Amputation	2
Local resection	2
Radiotherapy	**7 (18)**
20–30 Gy	5
56–60 Gy	2
Treatment for metastatic disease at presentation ($n = 24$)	
Sites of metastases	
Lungs	22 (91.7)
Lungs and bones	2 (8.3)
First-line chemotherapy	24 (100)
Median number of cycles	3 (1–6)
Adriamycin/cisplatin	20
Adriamycin/cisplatin/ifosfamide	5
Second-line chemotherapy	7 (29.2)
Median number of cycles	3 (1–6)
Ifosfamide/etoposide	2
Docetaxel/gemcitabine	4
Pazopanib	1
Surgery	13 (54.2)
Amputation	7
Local resection	5
Radiotherapy (20–30 Gy)	3 (12.5)

Discussion

This analysis from a tertiary care center presents the outcomes with a two-drug dyad chemotherapy, delivered in a resource-limited setting, where patients present late with large tumors and poor performance status.

Published literature shows the median age for osteosarcoma patients falls between 15 and 19 years with a male preponderance. This is similar to our study, where the median age was 18 years and the male-to-female ratio was 2:1.[1–3,10]

The most common symptoms (pain and swelling), most common sites of presentation (extremities), and stratification as per LD (80%) and MD (20%) in our analyses are similar to the global and national statistics.[1,2,10,11]

In contrast to the western population where patients present early with small tumor volumes, 53 (42%) of our patients presented for treatment more than 3 months after the onset of symptoms. This event is similar to the study by Nataraj et al from North India where 43% patients presented more than 4 months after the onset of symptoms.[10] Larger

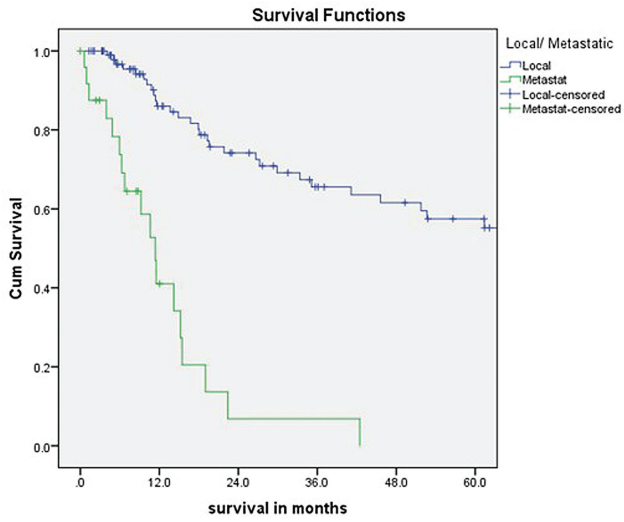

Fig. 1 5-Year Survival for patients with Localized Disease (Local) and Metastatic Disease (Metastat)

tumor volume is considered to be an adverse prognostic factor. Tumors greater than 12 cm were seen in 35 (28%) of our patients, similar to a study by Bajpai et al from Tata Memorial Hospital India, in which the median tumor size was 11.5 cm.[3]

Financial constraints influence management decisions, with 117 (92%) patients affording MRI for the primary tumor, while positron emission tomography (PET) CT was done in less than 5% patients.[13] Bone marrow biopsy was done for staging in limited patients predominantly with lung metastases or symptomatic for bony pain/raised alkaline phosphatase, who cannot afford to get a PET scan or bone scan. Fertility preservation counselling was done for all patients before the start of chemotherapy, but none consented for the same, in view of the additional costs associated with it.[14]

Multiagent NACT prior to local treatment helps downstage the disease, increase the probability of R0 resection, facilitate limb salvage surgery, and improve survival.[5,6] Response to NACT is considered to be an important prognostic factor with patients showing less than 10% viable tumor on histopathology having a significantly better survival.[12,15]

Osteosarcoma chemotherapy protocols mainly utilize a dyad of cisplatin and doxorubicin, with the addition of a third drug, either ifosfamide or HDMTX, which has been shown to improve the efficacy.[16,17] A recent meta-analysis by Anninga et al has demonstrated the superiority of three-drug regimens to two-drug regimens, and its equivalence to four drugs with lesser toxicity.[18]

Dyad chemotherapy using only two agents, AC, given every 3 weeks is the regimen used in our analysis as per our institutional protocol. Hematological toxicity (grades 3 and 4) with chemotherapy included anemia and neutropenia seen in 18 (18%) and 26 (26%) patients, respectively. Two patients had septic shock secondary to neutropenic sepsis. Patients at our center present with poor performance status and nutritional deficiencies as evident from the fact that 77 (61%) patients had BMI less than 18.5 at presentation. Due to social and financial barriers, these patients were unable to adhere to the support required to manage the toxicities arising from more intensive regimens. In our study, 83 (65%) patients report to tertiary care centers from rural areas, who show a poor compliance to treatment, with only 72 (73%) patients with LD completing the six cycles of chemotherapy and only 83 (84%) patients with LD undergoing surgery. In a study from Northeast India, 32% patients failed to complete preoperative chemotherapy and one-third of the patients did not undergo surgery. Only 23% of patients completed planned postoperative chemotherapy.[19] In an analysis on Ewing's sarcoma, patients from our institute, receiving alternating cycles of Vincristine/adriamycin/cyclophosphamide (VAC) and IE chemotherapy, compliance to treatment was poor. Primary tumor size greater than 8 cm ($p = 0.008$), completion of less than 15 cycles of chemotherapy ($p = 0.005$), and presence of MD ($p = 0.001$) were associated with inferior survival on multivariate analysis.[20]

Adjuvant chemotherapy is delivered after local surgery. Currently, there is no consensus for changing the chemotherapy regimen after a poor response to NACT due to failure

Table 5 Overall survival: univariate and multivariate Cox regression analysis for patients with localized disease ($n = 99$)

Variable	Univariate analysis			Multivariate analysis		
	HR	CI	*p* value	HR	CI	*p* value
Age >21 y	0.82	0.39–1.74	0.61			
Gender (male)	1.72	0.77–3.83	0.18			
Duration of presenting symptoms >6 mo	0.88	0.39–1.96	0.75			
Primary site (lower extremity vs. upper extremity)	2.02	0.82–4.95	0.12			
Primary tumor size <12 cm	0.28	0.87–0.9	0.03	2.22	0.79–6.21	0.12
No. of chemotherapy cycles: ≥6	0.54	0.25–1.14	0.10			
Underwent surgery	0.25	0.10–0.65	0.003	0.26	0.06–1.15	0.075
Necrosis grade 4 vs. 1	0.24	0.03–2.04	0.19			
Local vs. metastatic disease	3.87	2.11–7.09	0.001			

Abbreviations: CI, confidence interval; HR, hazard ratio.

in improving outcomes in patients who respond poorly to the regimen.[21] In one large, randomized trial, muramyl tripeptide added to postoperative chemotherapy was associated with a significant advantage in OS.[22] However, there is no consensus for its use due to the availability of only one randomized study and the lack of a statistical significance for the improvement in event-free survival (EFS). The European and American Osteosarcoma Study (EURAMOS-1) was conducted to test the improvement in outcomes, upon the addition of ifosfamide and etoposide to MAP in the postoperative setting in patients with less than 90% histologic response to preoperative chemotherapy. The study confirmed that more than three drugs were not useful.[23] Change of chemotherapy to IE in the adjuvant setting in our study was done for few patients with very poor histological and/or clinical response and good performance status.

Local treatment is planned in a multidisciplinary meeting after clinical and radiological response assessment. Local treatment may consist of limb salvage surgery or amputation.[24] Quality of life is essential for childhood malignancies where the aim is to provide cure with function preservation.[25] In our study, 65/83 (78%) patients in the surgery arm had undergone limb salvage surgery. Amputation is considered when negative margins cannot be achieved without compromising the functional outcomes. Limb salvage surgery with clear margins helps improve functionality, quality of life, and OS.[26,27]

Radiotherapy in this relatively radioresistant tumor is mainly limited for advanced, unresectable axial tumors where resection is likely to result in residual disease and cause unacceptable morbidity.[28] Postoperative radiotherapy is indicated for positive or close margins (>2 mm). Postoperative radiotherapy (45–54 Gy) at our institute is added for positive margins, and four patients received it following limb salvage surgery.

Recurrent osteosarcoma has poor outcomes, with distant metastases being more common than local recurrences as seen in our study.[29] Chemotherapy is the main modality of management and may include ifosfamide, etoposide, gemcitabine, docetaxel, platinum, pazopanib, etc., used alone or in combination.[4,30] Surgery may be considered for local recurrences and resectable disease. Radiotherapy may be preferred for local treatment of primary or oligometastatic sites.[4,31]

Patients with metastases at diagnosis are treated based on the disease burden, performance status, and with the aim to provide a good quality of life.[2,32] Patients with oligometastases and good response to chemotherapy are treated on lines of LD with chemotherapy followed by local therapy and additional radiotherapy for oligometastases, followed by consolidation systemic therapy.[1,4] In our analysis, patients with MD were predominantly treated with AC chemotherapy, with 13/24 (54%) patients undergoing surgery, predominantly consisting of amputation. The choice of regimen in second-line therapy is quite variable (►**Table 4**) and is based on patient profile and drugs used previously.

At a median follow-up of 50.4 months, the 3-year OS for patients with LD and overall cohort was 63, and 51%, respectively, while the 5-year OS for patients with LD and overall cohort was 53 and 43%, respectively. The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. For the MD, the 1-year OS was 41%, which dropped to 7% by 2 years.

In a study from TMH, Mumbai, at a median follow-up of 86 months, the 5-year OS with OGS-99 enhanced using a three-drug, non-HDMTX regimen was 60%. The 5-year EFS for OGS-99 and OGS-99 enhanced was 38 and 50%, respectively.[3] In another study from TMH, Mumbai, by Bajpai et al,[33] with the OGS-12 protocol, using a three-drug, non-HDMTX regimen, at a median follow-up of 34.31 (range: 2–60) months, in intention-to-treat (ITT) analysis, the 5-year EFS and OS were 56 and 75%, respectively; the same were 60 and 80% in per-protocol analysis. In a study from South India, using a three-drug non-HDMTX regimen, the 3-year OS was 54.6%.[11] Another study from North India, using a two-drug/-four-drug non-HDMTX regimen, reported a 5-year OS of 50%.[10] In HDMTX-based chemotherapy regimens, outcomes as reported from the west report a 5-year OS and EFS of 64.5 and 48.5%, respectively.[34] Another study from the west with HDMTX- based regimen reported 5-year OS and EFS of 63 and 57%, respectively.[5]

Thus, the majority of Indian studies[3,10,11] with non-HDMTX regimens, using two- or three-drug regimens, report a 5-year survival in the range of 50 to 60% and our study using a two-drug non-HDMTX regimen reports a 5-year survival of 53% for LD. However, one of the largest data on osteosarcoma from India, OGS-12 protocol,[33] sequentially using a three-drug non-HDMTX regimen reported excellent outcomes with 5-year OS of 75%, which is comparable to HDMTX-based regimens used in the west.[5,34] The better outcomes with the OGS-12 protocol[33] were attributed to the use of three active drugs, including ifosfamide with increased dose density and improved supportive care including prophylactic growth factors leading to improved compliance. The incidence of febrile neutropenia was 40%, and grade 3/4 thrombocytopenia and anemia were seen in 36 and 51% patients, respectively.

The poor outcomes in our study arise from various geographical, social, and financial barriers that patients from low- and middle-income countries face. These barriers lead to delayed presentation with advanced disease, a poor performance status, and poor compliance to treatment.[8] To improve outcomes in our patients, the addition of a third chemotherapy agent like ifosfamide, similar to OGS-12, may be considered for intensification of treatment.[3,11] However, patients need to be selected based on the baseline performance status, nutritional status, and social and financial resources of the individual patient for compliance with supportive care and more toxic treatment protocols. Awareness and educative programs for early detection, nutritional buildup, and diet management may further help intensify chemotherapy protocols and improve outcomes.

Various studies have reported old age, female gender, good histological response to chemotherapy (<10% viable tumor), size of primary tumor at presentation, tumor size, site, surgical resectability, and presence of metastases as prognostic factors.[35] In our study, on univariate analysis, the factors that were statistically associated with inferior survival in patients with LD included primary tumor greater

than 12 cm ($p = 0.03$) and exclusion of surgery ($p = 0.003$) for the management of the primary tumor. However, on multivariate analysis, none of these factors were found to be statistically significant. The presence of MD ($p = 0.001$) was found to be statistically associated with inferior OS.

The limitations of our study are that it was a single institute–based, retrospective analysis of a small number of patients. Details of toxicity arising from treatment were not precisely available. However, in view of the rarity of osteosarcoma, it is difficult to conduct a prospective randomized trial. Nevertheless, our study adds to the existing knowledge on epidemiology and clinical profile of the patients of osteosarcoma. It reports outcomes with a two-drug dyad chemotherapy in a real-world scenario and reports the challenges faced in a resource-limited setting.

Conclusion

In a resource-limited setting where patients present with large tumors and poor general condition, non-HDMTX-based regimens are easily tolerated with acceptable toxicity. Outcomes in our analysis with dyad chemotherapy were similar to other non-HDMTX-based chemotherapy regimens reported from India but were inferior to the OGS-12 protocol used in India and HDMTX-based regimens used in the west. Creating awareness among patients to seek medical attention early along with intensification of treatment by the inclusion of a third drug like ifosfamide for selected patients may help improve outcomes.

Ethics

Waiver was obtained from the institutional ethics committee (reference number GMCH/IEC/2024/1341) as this was a record-based analysis and did not involve any patient interaction or intervention.

Authors' Contributions

All the authors read and approved the manuscript and contributed to it.

N.G. contributed to the concept, data collection, data analysis, and preparation and finalization of the draft. K.D. contributed to the supervision of data collection and revision of the draft. S.K.G. contributed to the concept and revision of the draft. A.K.P. contributed to the concept and supervision of data collection. A.A. contributed to data collection and data analysis.

Patient Consent

None declared.

Funding

None.

Conflict of Interest

None declared.

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