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Original Article

Osteosarcoma in Children Younger than 5 Years of Age: A Single-Center Case Series from India Depicting Their Clinical Features and Outcomes with Review of Literature

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Abstract

Background Osteosarcoma in children £5 years old is extremely rare. There is very limited information available on this subset, especially from India.

Methods We retrospectively analyzed the clinical presentation and outcomes in children £5 years old with osteosarcoma diagnosed between January 2013 and December 2022. Staging was performed by non-contrast computerized tomography of thorax and bone scans. Treatment included OGS-2012 chemotherapy protocol with local control by surgery at 12 weeks.

Results Eleven of 588 children were £5 years (1.9%). The majority had lower limb tumors (81.8%) with metastases in 45%. Nine patients (localized-6, metastatic-3) received treatment. Six patients with localized disease completed treatment with limb-salvage surgery, of whom two had a metastatic relapse and one died due to an unknown cause. Of three metastatic patients, two progressed and one died (due to dengue) while on neoadjuvant chemotherapy. Eight episodes of febrile neutropenia and five episodes of mucositis were documented in treated patients.

Conclusion Osteosarcoma in children £5 years of age is extremely rare with predominant lower limb tumors and relatively inferior outcomes in treated patients.

Keywords
- osteosarcoma
- <5 years
- Outcomes

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Introduction

Although osteosarcoma is the most common primary malignant bone tumor in children, presentation in children ≤5 years is extremely rare, with this subset constituting 1 to 2.8% of the osteosarcoma cohort.[1,2] The information available on their presentation and outcomes is restricted to Surveillance, Epidemiology, and End Results (SEER) and Cooperative Osteosarcoma Study Group (COSS) cohorts treated on a high-dose methotrexate-based chemotherapy regimen. No reports are available from India, especially in the setting of a non-high-dose methotrexate-based protocol. Herein, we report the clinical profile and outcomes of histologically proven osteosarcoma in children ≤5 years registered at a single tertiary cancer care center in India from January 2013 to December 2022.

Case Series

Data regarding the demographic details, treatment, and outcomes were retrieved from the electronic medical records. The diagnosis was made based on morphology. Magnetic resonance imaging (MRI) scan was the imaging modality of the primary tumor, with staging done by non-contrast computed tomography (NCCT) of the thorax and bone scan. In metastatic disease, only oligometastatic lung metastases or other sites that were surgically resectable were treated. Children were treated on OGS-2012, a non-high-dose methotrexate-based chemotherapy protocol.[3] Local treatment was planned at 10 to 12 weeks after the start of chemotherapy. Limb salvage surgery (LSS) was done wherever feasible. Descriptive analysis was done on this study population.

There were 11 patients ≤5 years with osteosarcoma over a 10-year study period, which constituted 1.9% of the patients ≤15 years registered at our institute. The median age was 4 years (range, 3–5 years) with a male-to-female ratio of 2.6:1. The primary site was appendicular in the majority (90.9%, $n = 10$), which was predominantly the lower limb (81.8%, $n = 9$) and bones around the knee (63.6%, $n = 7$). Metastasis was present in 45.5% ($n = 5$), the site being lungs. The median tumor size was 8.4 cm (range, 3.5–16.7 cm), with nearly two-thirds having a tumor size ≥8 cm ($n = 7$).

Two children were palliated upfront due to multiple lung metastases. Nine patients were started on treatment, of which two had progression and one child expired due to dengue while on neoadjuvant chemotherapy. The remaining six patients underwent LSS, of which good histological response (>90% tumor necrosis) was seen in 50% patients ($n = 3$). Two of these six patients had a metastatic relapse. At a median follow-up of 5 years (range, 1.4–10.4 years), four patients passed away (disease: 2; dengue shock syndrome: 1; cause unknown posttreatment completion: 1), three were lost to follow-up, and two patients survived. There was one International Society of Pediatric Oncology (SIOP) grade 2 ototoxicity detected in a 4-year-old by pure tone audiometry. Grade 3/4 toxicities included eight episodes of febrile neutropenia and five episodes of mucositis in these nine patients. Details of the cases are presented in ►**Table 1**.

Discussion

Osteosarcoma in very young children, younger than 5 years, is extremely rare, with literature restricted to case reports and case series until two major groups, SEER and COSS, reported their three-decade cohorts comprising 49 and 28 patients, respectively. We found no data from India on this cohort. This study describes a single-center registration over a decade, with a prevalence of 1.9%, similar to reported western cohorts. The clinical characteristics of our subset have certain differences compared with the western cohorts.[1,2] Metastatic disease was seen in a higher proportion in our subset (45 vs. 12%: SEER; 14%: COSS; 22%: our institutional older cohort). Also, our cohort had a lesser proportion of patients with the proximal humerus as the site of primary (9%, $n = 1$) compared with western cohorts (39%)[2] as well as underrepresentation of telangiectatic histology ($n = 0$), which was pronounced in the western cohorts (SEER: 10.2%; COSS: 22%).[1,2] This needs further research on a `collaborative multicenter platform, as osteosarcomas in very young children are postulated to be biologically different.

Non-high-dose methotrexate-based chemotherapy was relatively well tolerated by these young children although outcomes were inferior in treated patients, which is similar to the inferior survival reported for this subset in western cohorts. No child underwent amputation in our subset, compared with the SEER and COSS cohorts with higher amputation rates of 55.2 and 29.6%, respectively, in very young children.[1,2] This is despite the fact that children with large tumors were comparable across all these cohorts. Rotationplasty was increasingly offered in our subset of very young children.

Osteosarcoma in very young children is exceedingly rare, with postulated biological differences compared with older children with osteosarcoma. This study, although limited by sample size, gives an outline of the cases from a single center in India treated on a non-high-dose methotrexate-based chemotherapy protocol. Reported outcomes are inferior in this subset, despite tolerability of chemotherapy as well as increased use of rotationplasty for local control.

Authors' Contributions

B.C.P. conceptualized and designed the study, designed the data collection instruments, coordinated and supervised the data collection, performed the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

V.R.M.G., M.P., A.P., A.G., M.R., B.R., A.J., N.P., and G.C. helped in drafting the manuscript and critically reviewed the manuscript for important intellectual content.

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Table 1 Details of children younger than 5 years with osteosarcoma ($n = 11$)

Number	Age (y)	Primary site	Histology	Localized/ metastatic	Baseline tumor size (cm)	Intent at baseline	Local therapy	Event	Final status
Case 1	5	Left distal femur	Osteoblastic	Localized	3.5	Curative	Intercalary resection with nail plate cement spacer	Follow-up	Alive with no disease at 1.5 y from diagnosis
Case 2	5	Right distal femur	Chondroblastic	Metastatic (lung, skip metastasis)	15	Curative	–	Metastatic progression on neoadjuvant chemotherapy	Death
Case 3	4.5	Left distal femur	Osteoblastic	Localized	5.8	Curative	Rotationplasty	Death (cause not known)	Death (cause not known)
Case 4	4	Right proximal humerus	Chondroblastic	Localized	15.5	Curative	Total excision of right humerus with surgical phocomelia	Metastatic relapse (lung, bone)	Lost to follow-up
Case 5	5	Right distal femur	Osteoblastic	Localized	8.4	Curative	Rotationplasty	Metastatic relapse (lung, lymph-node, adnexal)	Lost to follow-up
Case 6	4	Right distal femur	Osteoblastic	Metastatic (lung)	13.5	Curative	–	Progression in both primary and lungs on neoadjuvant chemotherapy	Lost to follow-up
Case 7	4	Left 9th rib	Osteoblastic	Metastatic (lung)	8	Curative	–	Death (post cycle 3 with dengue shock syndrome)	Death
Case 8	4	Right proximal femur	Osteoblastic	Localized	4.5	Curative	Rotationplasty	Lost to follow-up	Lost to follow-up 4 y after diagnosis
Case 9	5	Left proximal femur	Osteoblastic	Metastatic (lung)	12.7	Palliative	–	Upfront palliated	Death
Case 10	3	Right distal femur	Osteoblastic	Localized	16.7	Curative	Rotationplasty	Follow-up	Alive with no disease 10 y from diagnosis
Case 11	4	Proximal left tibia	Osteoblastic	Metastatic (lung)	5.4	Palliative	–	Upfront palliated	Death

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All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical Committee Approval
Ethical approval was not required as this is a limited-sample retrospective case series.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Patient Consent
Patient consent was not taken as this is a retrospective review of cases.

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Conflict of Interest
None declared.

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