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PAEDIATRIC OSTEOSARCOMA: EXPERIENCE IN A TERTIARY CARE CENTRE FROM NORTH EAST INDIA

Oncology

Munlima Hazarika	Department of Medical & Paediatric Oncology, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India.
Satya S Sarangi*	Department of Medical & Paediatric Oncology, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India. *Corresponding Author
Partha S Roy	Department of Medical & Paediatric Oncology, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India.
BJ Saikia	Department of Medical & Paediatric Oncology, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India.
Bibhuti Bhusan Borthakur	Department of Surgery, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India.
Anupam Sarma	Department of Pathology, Dr Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India.

ABSTRACT

This study aims to evaluate the clinico-demographic parameters of paediatric osteosarcoma in a cancer centre from North-East India. This retrospective analysis included children below 18 years with diagnosis of osteosarcoma from 2013 to 2017. Thirty one cases were registered during the study period. Twenty seven patients had localised disease & 4 had metastatic disease. Two-third of the patients belonged to rural background. Median age at presentation was 13 years. Male: Female was 1.4:1. Preoperative chemotherapy was used in 29 patients (alternating cycles of cisplatin+ifosfamide & cisplatin+doxorubicin in 66% and methotrexate-based regimen in 26%). Median overall survival (OS) was 13 months. High serum LDH (level > 345 U/L) was found to be negatively associated with OS ($p< 0.05$). Socio-economic issues resulting in poor treatment compliance and high loss-to follow-up rate are some of the major obstacles in achieving superior response and necessitate adoption of population specific treatment protocol.

KEYWORDS

Paediatric, Osteosarcoma, Demography, Survival Patterns

INTRODUCTION

In children and adolescents, the most common primary malignant tumour arising from bone is osteosarcoma (OGS). It constitutes 4% of all childhood malignancies [1.]. In the United States, approximately 400 new cases are diagnosed annually in age below 20 years [1]. The prevalence is slightly more common in males as compared to females with a peak age incidence of 16 years in boys and 12 years in girls [2].Surgery and chemotherapy are considered as the main cornerstones of therapy. In developed countries, patients with a localised disease have a disease free survival (DFS) and overall survival (OS) of more than 60% with current treatment protocols, whereas, metastatic patients have survival rates in the range of 30-40% [3]. But in developing countries like India, the situation is much worse due to various socioeconomic, cultural and logistic issues. Published data on paediatric osteosarcoma is very limited and hence, the exact magnitude and disease trend is not properly understood. The feasibility and tolerability of the treatment regimes used in Western population also needs to be properly analysed in our patient population.

The study was carried out to evaluate the demographic and clinical characteristics of paediatric patients with OGS at Dr B. Borooah Cancer Institute (BBCI), Guwahati.

MATERIALS AND METHODS

Study Design

This is a retrospective observational study to evaluate the demographic profile, clinical presentations, treatment compliance and survival pattern of paediatric osteosarcoma patients in the North-East Indian population.

Participants

Thirty one patients included in this dataset were hospitalized between January 2013 and December 2017. The inclusion criteria included are: 1) biopsy proven osteosarcoma, 2) all children or adolescent of age ≤ 18 years. Exclusion criteria included: 1) presence of other synchronous or metachronous tumours, 2) age > 18 years 3) patients with histologies other than OGS. This study received approval from the Institutional Ethical Committee. Signed written consent obtained from patient's guardian before entering the study.

Data Collections And Follow Up

Data were collected retrospectively from hospital based cancer registries, individual medical case notes, electronic patient records and pathology reports, including age, gender, performance status, size of primary tumour, serum lactate dehydrogenase (LDH) level, serum alkaline phosphatise (ALP) level, histological subtype, stage, site, socio-economic background, treatment regimen used, and post-operative histopathological details. Stage was determined according to the American Joint Committee on Cancer Staging System (AJCC), 7th Edition. High resolution CT scan and bone scan were done at baseline to stage the patient. Magnetic resonance imaging (MRI) was done to evaluate the primary lesion. The chemotherapy regimen varied from patient to patient, which included MAP protocol[Annexure 1], OGS protocol [4] and alternating cycles of Cisplatin @ 40mg/m2 D1-D3 plus Ifosfamide @1.8mg/m2 D1-D5 with Cisplatin @ 40mg/m2 D1-D3 plus doxorubicin @ 25mg/m2 D1-D3. The type of surgery (amputation, limb salvage or rotation-plasty), as well as the type of reconstruction in resected patients, was chosen depending on the location and the extension of the tumour, life- style and patient preferences. Survival status was determined from the date of registration for each patient at BBCI. The OS was defined as the time from the date of registration to the date of death or to the date of last follow-up for patients who had not died before the censor date. Follow-up was done every 3 months by telephone. The contents of follow-up are tumour progression, recurrence, metastasis and survival days.

Statistical Methods

Patient and demographic features were summarized using median/centiles, means and standard deviations (SD). To look for significance of difference between patient and treatment variables "independent sample t-test" was used. Survival curves were estimated with the Kaplan-Meier method. The associations of the various clinical parameters with survival were evaluated in univariable and multivariable Cox-regression models. In the multivariable model, all variables with a statistically significant univariate association were included. Hazard ratios (HR) and 95% confidence intervals (CI) were provided for univariable and multivariable Cox-regression models. A Cox proportional hazards model was fitted to all individual prognostic variables to determine their independent effect. Analyses were performed in SPSS 19.0 software.

RESULTS

Demography [Table1]

Between January 2013 – December 2017, 31 patients of paediatric osteosarcoma were registered at BBCI, Guwahati, Assam. Of these 31 patients, 4 had metastatic disease at presentation. Around 1/4th of patients (7/31) were referred from different centres. The median age of presentation was 13 years. Nineteen out of 31 patients (60%) were males & 12/31 (40%) were females. Ninety percent of patients had ECOG status of 1. The distance travelled by the patients to treatment center ranged between 10-600 kilometres, median being 190 kilometres. The median monthly family income was Rs 6000 with one fourth of the patients belonging to low socio economic class as per Modified Kuppuswami scale [Annexure2]. About 3/4th of the patients belonged to rural background.

Table 1: Demography

Characteristics (N= 31)	Frequency (%)
Distance from native place (in kms) Mean± SD, Range; Median, Q1-Q3	224±173, 10-600; 190, 80-300
Monthly Income (in Rs) Mean± SD, Range; Median, Q1-Q3	14129±13845,1000-50000; 6000, 3000-25000
Age in years Mean± SD, Range; Median, Q1-Q3 ≤ 13years : >13 years	13±3; 8-18 , 13; 11-15 17(55) : 14(45)
Sex Male: Female	19(60) : 12(40)
ECOG 1 : 2 : 3	28(90) : 2(6) : 1(4)
Locality Rural : Urban	24 (77) : 7 (23)
Type of cases Denovo : Referred form other centres	24 (77) : 7 (23)

Disease Characteristics [table2]

Most of the patients presented with bulky tumour. The median size of primary tumour was 10 cm (Range 6 – 30 cm). Femur was the most common site of presentation followed by tibia, fibula and humerus. One out of 31 patients had axial location. In rest of the cases the location was appendicular skeleton. Osteoblastic osteosarcoma was the most common histology found in 29 out of 31 of patients (93%). The median LDH and ALP was 345 U/L (Range 167 - 560) and 236 IU/L (Range 124 - 398) respectively.

Table2: Disease Characteristics

Characteristics (N= 31)	Frequency (%)
Site Femur : Tibia : Fibula : Humerus : Pelvic	16 (51) : 11 (37) : 2 (6) : 1 (3) : 1 (3)
Site group Axial: Appendicular	1 (3) : 30 (97)
Stage Localized : Metastatic	27 (88) : 4 (12)
Size of primary (cms) Mean± SD, Range; Median, Q1-Q3 ≤ 10cm : >10cm	10 ± 4, 6 – 30, 10, 9 – 12 17 (55) : 14 (45)
Histology Osteoblastic: Chondroblastic	29 (94) : 2 (6)
Serum LDH (U/L) Mean± SD, Range; Median, Q1-Q3 ≤ 345: >345	369 ± 100,167-560; 345, 299-456 18 (58) : 13 (42)
Serum ALP (IU/L) Mean± SD, Range; Median, Q1-Q3 ≤ 236 : >236	248±64, 124-398; 236, 198-298 17 (55) : 14 (45)

Treatment Characteristics [table3]

Twenty seven out of 31 (87%) patients were treated with radical intent. Sixty six percent (21/31) of patients received alternating cycles of cisplatin plus ifosfamide and cisplatin plus doxorubicin protocol. Sixteen percent (5/31) patients were treated with MAP protocol and 10 % (3/31) with OGS protocol. Of the 22 patients eligible for neoadjuvant chemotherapy (NACT), 15 (70%) patients completed the desired protocol whereas rest 30 percent did not complete NACT. Surgery was performed in 21 patients out 31 (67 %), of which 14 (66%) underwent amputation and rest one third patients had limb salvage surgeries. Only one patient out of 21 had a positive margin whereas 8/21 had negative margins. In rest 12 patients margin status was unknown. Fifty three percent (8/15) of patients had more than 90% necrosis (considered as *good histologic response*) to neoadjuvant chemotherapy. Of these, 5 /10 (50%) patients received alternating cycles of cisplatin plus ifosfamide and cisplatin plus doxorubicin protocol, 2/5 (40 %) received MAP protocol and 1/3 (33%) received OGS protocol.

Table 3 : Treatment Parameters

Characteristics (N= 31)	Frequency (%)
Intent Radical : Palliative	27(88) : 4 (12)
Protocol MAP: OGS: Cis + Ifosfamide ;others :No treatment	5 (19) :3 (9) :21 (66) :1 (3) : 1 (3)
NACT compliance Yes : No : Not applicable	15 (48) : 7 (22) : 9 (30)
Surgery Yes : no	21 (66) : 10 (34)
Adjuvant CT compliance Yes : no	7 (23) : 24 (77)
Type of surgery (N- 21) Amputation : Limb salvage	14 (66) : 7 (33)
Margins status (N- 21) Positive : Negative: Not known	1 (5) : 8 (38) :12 (57)
Histology Necrosis >90% :<90%: Not known: Not applicable	8 (27) : 2 (6) : 2 (6): 19 (61)

Survival Analysis [table4]

At the time of study analysis, 7 /31 (23%) were alive, 14/31 (45%) were dead, 3/31 (9%) were lost to follow up without disease and 7/21 (23%) were lost to follow up with disease. The median progression free survival (mPFS) was 2 months [Figure 1] and median OS was 13 months (2-23 months) [Figure 2] with a median follow up of 12 months. When the OS was compared between various sub groups [Table 5a,b,c],only in Serum LDH there was a statistically significant difference present (≤ 345: >345; P <0.05) [Table 5c]. No statistical significance differences were observed in all other subgroups.

Table 4 : Survival Analysis

Characteristics (N= 31)	Frequency (%)
Status at last Follow up Alive : Dead : LFU with disease ; LFU without disease	7 (23) :14 (45) : 7 (23) : 3 (9)
Progression free survival (months) Mean± SD, Range; Median, Q1-Q3	10 ± 9, 1-52; 2, 1 – 14
Overall survival (months) Mean± SD, Range; Median, Q1-Q3	14 ± 12 , 1- 52; 13 , 3 – 19

Table 5 A: Overall Survival Difference As Per Subgroups

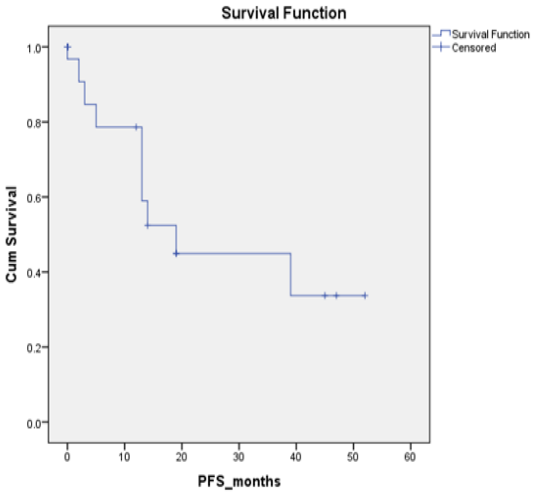
Parameters	OS in months	p value
Age		
< or equal to 13	**17**	NS
>13	**10**	
Sex		
Male	**14**	NS
Female	**13**	
ECOG		
1	**15**	NS
2	**1**	
3	**1**	
Size of primary		
< or equal to 10 cm	**15**	NS
>10 cm	**12**	
Stage		
Localised	**15**	NS
Metatstatic	**1**	

Table 5 B : Overall Survival Difference As Per Subgroups

Parameters	OS in months	p value
Site		
Femur	**18**	NS
Humerus	**3**	
Tibia	**10**	
Fibula	**11**	
Site group		
Axial	**1**	NS
Appendicular	**14**	
Histology Type		
Osteoblastic	**14**	NS
Chondrobalstic	**7**	
Protocol used		
MAP	**23**	NS
OGS	**6**	
CDDP + Ifos	**13**	
SE status		
Rural	**13**	NS
Urban	**15**	

Table 5 C : Overall Survival Difference As Per Subgroups

Parameters	OS in months	p value
LDH		
< or equal to 345	**17**	p<0.05
>345	**9**	
Surgery type		
Amputation	**15**	NS
Limb Salvage	**22**	
Margin status		
Positive	**4**	NS
Negative	**20**	
Unknown	**5**	
ALP		
< or equal to 246	**14**	NS
> 246	**13**	
Histology necrosis		
<90%	**17**	NS
>90%	**28**	
Unknown	**8**	

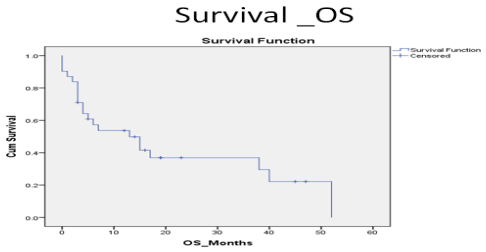


Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
14.616	3.703	7.358	21.873	2.000	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

Figure 1 Progression Free Survival



Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
21.195	4.053	13.252	29.138	13.000	5.298	2.616	23.384

a. Estimation is limited to the largest survival time if it is censored.

Figure 2 Overall Survival

DISCUSSION

Osteosarcoma considered as the most common primary malignant bone tumour [5] occurring primarily in adolescent age group that coincides with the growth spurt of young boys and girls [6].It mainly involves the long bones of the body, and less commonly in axial skeleton. Recent evidence [7] suggests the management protocol should have pre-operative chemotherapy followed by surgery and additional adjuvant chemotherapy. Earlier studies [8] showed no difference in survival with the NACT approach in comparison to upfront surgical approach. However, NACT followed by surgery with additional adjuvant chemotherapy treatment protocol provides better logistics (time to develop prosthesis for limb salvage procedures) and also helps in evaluating the pathological response to NACT, which is correlated with survival [9]. In the last decade, numerous studies on osteosarcoma were published from India. Majority of these studies included both adult as well as pediatric population. Pathak *et al*. in 1993 initially published their data on 29 patients with high-grade OGS, who received sequential adriamycin and cisplatin as adjuvant therapy after definitive surgery. The relapse-free survival was 72%, and OS for the entire group was 69%, which was superior to outcomes in historical controls treated with surgery alone.[10]

In our study, the median age of presentation was 13 years with a male: female ratio of 1.4:1. Our findings are comparable to a study from South India, which reported a female predominance [11]. Studies by Puri et al., and Gulia et al., have reported mean age at presentation ranging from 16 to 22 years with conflicting gender preponderance. [12][13]

The most common site of involvement was femur (as also seen in study from South India) [11]. The median size of the primary tumour was 10 cm, which is comparable to the study done by Bapai et al., with mean primary tumour size of 10.45 cm [14]. Osteoblastic histology or conventional osteosarcoma was the most common histology, similar to South Indian Study [11]. However, a study done by Laskar et al.,[15] reported chondrobalstic variant to be the most common histology. This difference in the histology pattern is because of different patient population in the study by Laskar et al., which includes patients with tumour arising from Head-Neck region. The serum LDH and serum ALP values were high in majority of our patients with a median value of 345 U/L and 236 IU/L respectively. When we did a subgroup analysis by using the median value as cut off, the patients with pre-treatment serum LDH level less ≤ to 345 U/L had significantly better survival than those having higher value. Prognostic significance of pre-treatment serum LDH has been observed by other studies also [16-17].

About 3/4th of patients were from rural locality and they had to travel a median distance of 190 km to reach to the hospital for treatment at frequent interval. Long distance from treatment centre together with financial burden due to frequent hospital visit are important causes of treatment discontinuation.[18] In our study, 32 % patients have not completed the planned pre-operative chemotherapy and one third of

patients had no surgery. Relief in symptom burden after pre-operative chemotherapy, fear and stigma associated with amputation of limbs, in addition to the financial and logistic issues are associated with refusal to surgery. Lost to follow-up rate in our study was 33%. Only 23% of patients completed planned post-operative chemotherapy.

The most common chemotherapy regimen used in this study was alternating cycles of cisplatin plus ifosfamide and cisplatin plus doxorubicin. Non-methotrexate based regimens are most commonly used regimens in majority of the cancer centre in India for high grade osteosarcoma. [19]

The median progression free survival is 2 months which is fairly less as compared to other studies reported in literature (median PFS ranges from 26 to 40 months) [20-22]. The most likely reason could be due to the high lost to follow-up rate in our study, as lost to follow-up patients are considered as events for PFS analysis. The median OS was 13 months for the entire study population which is yet again less than reported rate in literature on Western and Indian population [20-22]. Inclusion of patients with metastatic disease and poor compliance to treatment regimen might be related to low survival rate in our study.

Strength Of Study

In the dearth of data for paediatric osteosarcoma patients from India, ours study has provided some insight, which to the best of our knowledge is the only study from the North-Eastern part of India. This study has included both localised and metastatic disease. We have tried to highlight the real world scenario for these paediatric patient populations which is relatively different from randomised trials. It also tried to compare the efficacy of different chemotherapy regimens used.

Limitations

Ours study being retrospective one has got various limitations. Small sample size might have resulted in non-significant p-values for many sub-group analyses. High loss to follow-up rate and shorter duration of median follow-up are amongst the other limitations of the study.

CONCLUSION

The study provides valuable insight regarding presentation and management of a rare paediatric tumour from Indian subcontinent. Socio-economic issues resulting in poor treatment compliance and high lost-to follow-up rate are some of the major barrier in achieving better responses to treatment. There is an urgent need to design and implement a specific population based protocol to achieve better outcome.

Annexure 1

Doxorubicin, cisplatin, and high-dose methotrexate (MAP) followed by surgery and MAP for nonmetastatic osteosarcoma (control arm, COG AOST 0331)

Weeks	Agents	Dose	Days
Induction MAP (weeks 1 through 10)			
1, 6	Doxorubicin	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	1 and 2
4, 5, 9, 10	High-dose methotrexate	12 grams/m^2 IV over four hours*	1
	Leucovorin rescue	15 mg (approximately 10 mg/m^2) every six hours IV or orally for 10 doses¶	Starting 24 hours after beginning high-dose methotrexate
Surgery (week 11)			
11	Resection or amputation		
Postoperative MAP (weeks 12 through 29)			
12, 17	Doxorubicin$^\Delta$	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	1 and 2
22, 26	Doxorubicin$^\Delta$	37.5 mg/m^2 per day IV over 24 hours	1 and 2
15, 16, 20, 21, 24, 25, 28, 29	High-dose methotrexate	12 grams/m^2 IV over four hours	1
	Leucovorin rescue	15 mg (approximately 10 mg/m^2) every six hours IV or orally for 10 doses	Starting 24 hours after beginning high-dose methotrexate

IV: intravenous.
* Some pediatric oncologists limit the methotrexate dose to 20 grams total (Meyers, PA, et al. J Clin Oncol 2005; 23:2004).
¶ Leucovorin doses adjusted depending on blood methotrexate levels.
Δ Dexrazoxane can be given with doxorubicin, although osteosarcoma-specific data are not available.

Created With Data From:

1. National Cancer Institute Clinical Trials. Phase III randomized study of neoadjuvant induction therapy comprising doxorubicin, cisplatin, and high-dose methotrexate (MAP) followed by surgery and adjuvant maintenance therapy comprising map alone versus map and peg-interferon alfa-2b or MAP combined with ifosfamide and etoposide in patients with resectable high-grade osteosarcoma; available at: https://clinicaltrials.gov/ct2/show/NCT00134030?term=AOST+0331&rank=1, accessed February 26, 2016.

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Annexure 2

- Modified Kuppuswamy's Socioeconomic Status Scale

A	Education of head of family	Score
1	Profession or Honours	7
2	Graduate or post graduate	6
3	Intermediate or post high school diploma	5
4	High school certificate	4
5	Middle school certificate	3
6	Primary school certificate	2
7	Illiterate	1

B	Occupation of head of family	Score
1	Profession	10
2	Semi-Profession	6
3	Clerical, Shop-owner, Farmer	5
4	Skilled worker	4
5	Semi-skilled worker	3
6	Unskilled worker	2
7	Unemployed	1

C	Family income per month(in Rs)	Score
1	≥19575	12
2	9788-19574	10
3	7323- 9787	6
4	4894- 7322	4
5	2936-4893	3
6	980-2935	2
7	≤979	1

	Total Score	Socioeconomic class
	26-29	Upper (I)
	16-25	Upper Middle (II)
	11-15	Lower middle (III)
	5-10	Upper lower (IV)
	<5	Lower (V)

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