Clinico-pathological Study of Limb Salvage Surgery for Osteosarcoma: Experience in a Rural Cancer Center

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Received: 4 August 2014 / Accepted: 16 August 2016 / Published online: 30 August 2016
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Abstract Although recent multimodality therapeutic protocols have led to improved survival in osteosarcoma (OS), the outcome still remains dismal. Ongoing international multicentric trials on OS aim to randomize patients for optimum management, based on histological response to NACT. The pathologic response to neoadjuvant chemotherapy (NACT) is the most important factor predicting prognosis. In this study of 23 cases of limb salvage surgery post neoadjuvant chemotherapy, mean age was 18.3 years, with male predominance. 65.5 % cases were conventional OS. Histologic assessment of chemotherapeutic effect done by Huvos grading revealed good response (Huvos III and IV) in 15 (65.2 %) and poor response (Huvos I and II) in eight (34.8 %). A scoring based on MRI with a scale of 1–6 was compared with histologic response. Five (62.5 %) of poor responders showed score of >3 and 73.3 % of good responders showed ≤3. Dose intensity of NACT was calculated and correlated with the histological response. 53.3 % of good responders showed ARDI > 0.9. Five (21.7 %) developed local recurrence and 10(43.4 %) had pulmonary metastasis. Adoption of more aggressive treatment modalities may ensure better histologic response and longer event free survival.

Keywords Osteosarcoma · Limb salvage surgery · Histological response osteosarcoma · Neoadjuvant chemotherapy · Huvos scoring system · Radiological scoring osteosarcoma

Introduction

Osteosarcoma (OS) is the most common, non-hemopoietic, primary malignant tumor of bone [10]. With advent of newer chemotherapy drugs and prosthesis, the trend has shifted from amputation to limb salvage surgeries (LSS) for OS [9]. The pathologic response to neoadjuvant chemotherapy (NACT) is the single most important factor predicting prognosis [8]. Hence, a retrospective study was done on LS specimens of OS with the purpose determining the pre-chemotherapy clinical, radiological, and pathological factors that may have influence on the pathological response and to study the post-chemotherapy pathological changes in LS specimens.

Material and Methods

A retrospective study including all LSS specimens of OS received in Department of Pathology, Malabar Cancer Centre, Thalassery between September 2011 and January 2014 was done. Excised small bone specimens, amputation specimens, and other bone tumors were excluded. Relevant clinical information like age, sex, symptoms, anatomical location of lesion, history of pre-existing bone lesions, and number of cycles of NACT were collected. The average relative dose intensity (ARDI) of chemotherapy was calculated. Dose intensity is a measure of the amount of drug delivered per unit of time, generally expressed as milligram per square meter per week.

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Table 1 Radiological scoring system for prognostic factors in OS pre NACT

	0	1	2
Size of tumor (maximum diameter)		</ 8 cm	> 8 cm
Cortical destruction	A	P	
Soft tissue involvement	A	P	
Neurovascular bundle involvement	A	P	
Joint involvement	A	P	

A absent, P present

Relative dose intensity (RDI) is calculated by dividing the DI of the administered regimen by the DI of the drug in the standard regimen. Average relative DI corresponds to the mean DI of combined agents [11]. A scoring system of pre-chemotherapy radiological prognostic factors on MRI was devised to correlate with histological response (Table 1). The LS specimens were examined and an entire representative slice of the tumor was mapped using a grid pattern diagram to indicate the site for each tumor block and sampled [21]. Response to chemotherapy was quantified by Huvo's tumor necrosis grading system [16, 17]. No human or animal rights were violated during the study.

Statistics

No statistical method was applied because of the small number of cases studied.

Results

Twenty-three cases of LS surgery for OS were included in the study. Majority of the patients presented in the second decade of life (78 %), with a mean age of 18.3 years. Male: female ratio was 2.3:1. Upper end of tibia (43.5 %) and lower end of femur (39.1 %) were the most affected sites. Diagnostic

biopsy done from the tumor showed conventional OS (65.3 %) in majority of cases and two cases each of OS—chondroblastic and fibroblastic variants; including two cases where pleomorphic sarcoma was suspected.

Radiological (MRI) diagnosis was OS in all cases (Fig. 1). Radiological prognostic score was ≤ 3 in 14 (60.9 %) cases and > 3 in 9 (39.1 %) cases.

Lung metastasis was seen in five cases on presentation, out of which three were bilateral. The patients with metastatic disease at presentation were 14–23 years of age, with primary tumor in femur (3), tibia (1), and humerus (1). The size of the primary in these cases ranged from 7 to 25 cm, with an average MRI score of 4.

All patients were given six cycles chemotherapy; with 3–6 cycles of NACT. The drugs used were ifosfamide, adriamycin, and cisplatin. Average preoperative ARDI was calculated to be 0.856. ARDI > 0.9 was seen in 42.9 % cases, 0.75 to 0.9 in 38.1 % cases, and < 0.75 % in 19 % of cases.

Limb salvage surgery followed by reconstruction with custom made prosthesis was done in all cases. Frozen section for margin status was done in 12 cases. Margin positivity is seen in one case.

On pathological examination of LS specimen, residual tumor was present in 13 (56.5 %) and no residual tumor in 10 (43.5 %) (Fig. 2). Huvo's grading system was applied for assessment of response to chemotherapy. Complete response grade IV was seen in 43.5 % cases, good response grade III in 21.7 % cases and poor response grade I and II in 34.8 % cases (Fig. 3). 44.4 % of OS, 100 % of fibroblastic OS showed complete response; whereas both chondroblastic OS showed good response. Chemotherapy-induced changes seen were necrosis/fibrosis in 23 (100 %), increased vascularity in five (21.7 %) and osteosclerosis in ten (43.5 %) (Fig. 4).

Local recurrence was seen in five (21.7 %) cases in a mean period of 6 months. (Fig. 5). Two of these cases were treated with wide excision and amputation was done in one case. Two of these patients are doing well to date

Fig. 1 a MRI- osteosarcoma distal end femur. b CT-thorax- lung metastasis

Fig. 2 Specimens of limb salvage surgery-**a** with residual tumor **b** with necrotic area

(mean follow-up period 5 months). Four cases with recurrence also had lung metastasis; two of these patients had lung metastasis on presentation. Out of five cases with metastasis on presentation, two cases developed local recurrence later; and out of 18 cases without any distant metastasis at presentation, three developed local recurrences.

Lung metastasis was seen in a total of ten (43.5 %) cases, four had metastasis on presentation. Lung metastasis developed on follow up in six cases. Bilateral lung metastasis was seen in five cases. Metastatectomy was done in one case. Four patients died, all had lung metastasis and three had local recurrence. The remaining cases were lost to follow-up.

Discussion

Osteosarcoma arises from primitive bone-forming mesenchymal cells and is the most common primary bone malignancy. Among childhood cancers, osteosarcoma occurs eighth in general incidence. Osteosarcoma has a bimodal age distribution, having the first peak in the 10–14-year-old age group coinciding with the pubertal growth spurt and the second peak in older adulthood, frequently related to Paget's disease. The incidence of osteosarcoma is higher in males than in females.

Osteosarcoma commonly occurs in the metaphysis of long bones, the most common sites being distal femur (42 %), proximal tibia (19 %), and the proximal humerus (10 %) [23].

Amputation, once the mainstay of treatment of malignant bone tumors, now is used infrequently. Most patients are candidates for limb-sparing procedures because of effective chemotherapeutic agents and regimens, improved imaging modalities, and advances in reconstructive surgery with significant improvement in long-term survival. [9] Nevertheless, recurrent disease still occurs in about 30–40 % of patients and more than 70 % of them die of their tumor, despite second-line treatment [2]. This and the variability in the behavior of OS make evaluation of known prognostic factors essential for predicting survival.

Currently, the histological response to chemotherapy is the single most important indicator of prognosis [7]. This is expressed as percentage of necrosis, with a 4-part grading system (Huvos et al). The hallmark of osteosarcoma necrosis is the dropout of neoplastic cells. Acellular tumor-produced matrix (i.e., osteoid, bone, and cartilage) remains in areas previously occupied by viable tumor. Residual matrix is frequently accompanied by cellular debris and an ingrowth of rudimentary granulation tissue, hemosiderin deposition, and/or fibrosis of varying density [23]. Chemotherapy-induced necrosis of 90 % or more has a greater than 90 % 5-year disease-free survival, while

Fig. 3 **a** OS post chemotherapy: osteoid, no viable tumor; H&E 4X. **b** OS- Residual tumor cells present; H&E 10X

Fig. 4 **a** Chemotherapy-induced changes: necrosis H&E 10X. **b** Chemotherapy-induced changes: fibrosis H&E 4X

less than 90 % necrosis has less than 15 % 5-year disease-free survival [22, 24]. In our study, 65.2 % of cases showed ≥ 90 % necrosis (Huvos grade III and IV); whereas 34.8 % showed < 90 % necrosis (Huvos II) [1, 15, 22] (Fig. 6).

Osteosarcoma typically appears as a mixed radiodense and lytic lesion arising in an eccentric manner from the metaphyseal bone. There is frequently mass extension into the adjacent tissue. Cortical destruction and periosteal reaction are common with sunburst appearance and Codman's triangle [12]. The findings on MRI of tumor size > 8 cm, cortical break, periosteal reaction, soft tissue, and joint involvement have poor outcome. Correlating the radiological score with histological response, it was observed that lower the score, better was the outcome. Seventy-three percent of cases with favorable response on histology had radiological score of ≤ 3 ; while 62 % of cases with poor response on histology had radiological score of > 3 . Pre-chemotherapy radiological parameters correlated well with occurrence of necrosis (Table 2) [3].

The concept of NACT was pioneered at Memorial-Sloan Kettering Cancer Centre. The goals of NACT are threefold: the immediate treatment of micro-metastatic

disease, limb preservation, and assessment of response to chemotherapy. In the present study, all patients received 2–6 cycles of neoadjuvant chemotherapy [13]. Three drugs were used—cisplatin, doxorubicin, and ifosfomide. Average ARDI of NACT was 0.856. Few studies in literature have correlated ARDI of chemotherapy of OS with histological response [19]. Majority (53.3 %) of patients who showed favorable response had ARDI of ≥ 0.9 [13] (Table 3). However, a number of other parameters that may affect the impact of chemotherapy on any particular tumor, including drug scheduling, resistance mechanisms, and pharmacodynamics influences.

Extensive gross and histologic examination with specimen mapping is required for accurate assessment of percentage of necrosis. When present, residual viable tumor was preferentially found at the interface of tumor and normal anatomic structures—“sanctuary sites” [24]. Fibrosis, granulation tissue, and inflammation were the various chemotherapy-induced changes seen. Necrotic areas were often seen replaced by fibrosis in the absence of viable tumor cells in cases where interval between surgery and chemotherapy was longer than 3 weeks. The biggest challenge to the surgical pathologist is the interpretation of small foci of atypical cells with hyperchromatic nuclei, smudged and clumped chromatin, and vacuolated cytoplasm. The current approach is to conservatively interpret them as “viable” tumor cells for purposes of grading and management [6].

Adverse prognostic factors recorded in literature include detectable metastases at diagnosis, age > 40 years, non-extremity localization, large tumor volume, elevated serum ALP or LDH, and a poor histological response to preoperative chemotherapy [25]. Recent studies on biomarkers by immunohistochemistry in OS have proved

Fig. 5 FNAC: OS recurrence Pap 40X

Fig. 6 Comparison of histological response in the present study with other studies. CR complete response; GR good response; PR poor response [1, 15, 22]

evidence of HIF-1 α and COX-2 protein expression is associated with the pathological response and outcome in OS patients [5].

Lung metastasis was seen in 10 (43.5 %) cases. Metastasis at presentation was seen in five (21.7 %) cases which is considered one of the most important prognostic factors for survival [1]. Patients should be followed at 3-month intervals until 3 years after the end of treatment, then at 6-month intervals until 5 years and at 8–12 month intervals until 10 years after the end of treatment. Examinations must include chest radiological analyses.

A recurrence rate of 21.7 % was recorded in the study period, which is comparable with that in Indian studies [18]. However, no correlation with known prognostic factors was attempted because of the retrospective nature of the study and the limited number of cases involved. In a developing country like India, factors like limited resources, delay in surgery, drug resistance, and poor patient compliance contribute to poor outcome of patients in spite of use of the same multimodality treatment protocols adopted in the developed countries [14]. This substantiates the need for larger prospective multicentric

studies with biomarker analysis in India to evaluate factors that influence local and systemic recurrence [20]. Ongoing challenges include tailoring chemotherapy to the individual risk of relapse and the development of biologically driven treatment strategies [4].

Conclusion

The challenge in OS stems from the extreme variability from one tumor to the next, making it unlikely that a single target approach would be able to address all or even a majority of patients. Awareness, education, and proper referral patterns serve to minimize avoidable errors in diagnosis and treatment. After introduction of LSS, although an initial improvement in survival (20–60 %) was noted; results have remained stationary for the past 30 years. New strategies are urgently required to improve the outcome in OS. Histological response to chemotherapy is the basis for randomization of patients for different

Table 2 MRI score vs Huvos grade cross tabulation

MRI score vs Huvos grade cross tabulation					
		Huvos_grade		Total	
		CR + GR	PR		
		Count	Count	Count	%
MRI score	≤ 3	11	3	14	60.9 %
		73.3 %	37.5 %		
	> 3	4	5	9	39.1 %
		26.7 %	62.5 %		
Total		15	8	23	100.0 %
		100.0 %	100.0 %		

Table 3 ARDI vs Huvos grade cross tabulation

ARDI vs Huvos grade			
Average RDI	Huvos grade		Total
	CR + GR	PR	
≤ 0.75	2 13.3 %	2 25.0 %	4 17.4 %
0.76–0.89	5 33.3 %	2 25.0 %	7 30.4 %
≥ 0.90	8 53.3 %	4 50.0 %	12 52.2 %
Total	15 100.0 %	8 100.0 %	23 100.0 %

chemotherapy protocols in large ongoing multicentric trials like EURAMOS. Larger prospective studies are required in the Indian context to determine the influence of various factors on outcome of OS patients.

Acknowledgments We acknowledge the invaluable help of the teaching and technical staff of department of Pathology, Malabar Cancer Centre and dedicate this article to the young patients suffering from osteosarcoma on whom this article is based.

Conflict of Interest The authors declare that they have no conflict of interest.

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