ORIGINAL ARTICLE

Patterns of care and outcomes of adult osteosarcoma in a tertiary care cancer centre in Pakistan

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Abstract

Objective: To present our experience of treatment outcomes in adult osteosarcoma patients.

Methods: The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data related to 74 adult patients with osteosarcoma from 1995 to 2009. The treatment plan consisted of surgery preceded by neo-adjuvant chemotherapy followed by adjuvant chemotherapy. SPSS 16 was used for statistical analysis.

Results: Of the 74 patients in the study, 58(78%) were in the 18-29 age group with an overall male-to-female ratio of 3:1. The commonest site of disease was femur, 30 (43%). Of the 66(89%) patients undergoing definitive surgery, 59(89.4%) had amputation. The remaining 7(10.6%) limb salvage operations were in the neo-adjuvant chemotherapy group. Good histopathological response rates in high-dose methotrexate containing regimens and other regimens were similar with an overall good response rate of 18/51 (35%). The commonest site of relapse was lung. Twelve out of 27 (44%) patients with lung-only metastases underwent successful metastatectomy. For patients with localised disease at presentation 3-year event-free survival was 30%, and 3-year overall survival was 71%. For patients with metastases at presentation 3-year overall survival was 45%. Median overall survival for patients receiving high-dose methotrexate and other regimens was 1.7 years vs 2.9 years.

Conclusion: Adult osteosarcoma treated with cisplatin/doxorubicin based chemotherapy and surgery had good outcomes. The role of high-dose methotrexate in adult osteosarcoma remains uncertain.

Keywords: Chemotherapy, Methotrexate, Osteosarcoma, Overall survival, Pakistan. (JPMA 64: 1166; 2014)

Introduction

Osteosarcoma is a primary malignant bone tumour. It is an uncommon tumour in adults and accounts for less than 1 percent of all cancers diagnosed annually in the United States.[1] Osteosarcoma has a bimodal age distribution with a major peak incidence in early adolescence and later in adults over the age of 651. There is scarcity of information about adult osteosarcoma. According to the Surveillance, Epidemiology and End Results Programme (SEER) data analysis, osteosarcoma in the age group of 25-59 years comprises approximately 28% of the reported cases.[1] At all ages, males are affected more frequently than females. In young patients, it most often arises in the metaphysis of long bones, such as the distal femur, proximal tibia, and proximal humerus.[1,2] In the elderly, osteosarcoma occurs more commonly in axial locations and in areas that have been previously radiated or have underlying bone abnormalities. At diagnosis, osteosarcoma is localised in one bone site in 80% of the cases and presents with metastases in about 20% of the patients. Lung is the most common metastatic site, followed by bone. Other metastatic sites are uncommon.[2]

Current standard of treatment includes preoperative/neoadjuvant chemotherapy (NAC) followed by surgery and postoperative/adjuvant chemotherapy (AC). With such multimodality therapy, at least two-third patients with non-metastatic extremity osteosarcomas tend to be long-term survivors and up to 50 percent of those with limited pulmonary metastases can be cured of their disease. Extra-pulmonary metastases and multifocal osteosarcoma constitute a major problem. The aim of surgery is to completely resect the tumour to produce the minimum risk of local recurrence. Surgery for local disease can be carried out with an amputation or limb salvage depending on location and extent of disease and response of primary tumour to preoperative chemotherapy.[2] The long-term survival rate of patients with osteosarcoma was 10-20% before the 1970s when treatment was mainly limb amputation. Over the past three decades, the development of surgical techniques and effective multi-agent systemic chemotherapy has led to improvement in disease-free and overall survival rates of upto 60-70%.[2] NAC induces tumour necrosis in the primary tumour which facilitates surgical resection, particularly limb salvage procedures, and also provides early treatment of micro metastatic diseases. Patients with tumour necrosis in

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excess of 90% are classified as good responders while those with tumour necrosis less than 90% are classified as poor responders.[2] The degree of tumour necrosis is used as a marker of chemo-sensitivity and has proven to be an important prognostic factor.[3,4] However, research has been unable to confirm that altering the AC regimen in poor responders improves overall outcomes.[5,6] Most widely applied and studied NAC and AC regimens consist of a combination of cisplatin, doxorubicin with/without high-dose methotrexate and/or ifosfamide. Various study groups have shown that these drug combinations have the best 5-10 year survival rates of 70-72%.[2,7] Patients with synchronous pulmonary metastatic disease are also treated with the same chemotherapy agents followed by resection of primary and metastatic disease albeit with poorer results. Multiple numbers of lung nodules and metastasis identified at the initial presentation of disease predict poor response.[8] However, there are studies showing complete surgical remission following pulmonary metastatectomy as the main prognostic factor. It has been shown that metastatectomy preceded or followed by chemotherapy improves long-term survival in recurrent pulmonary metastasis as well.[9]

There is paucity of comprehensive population-based data on occurrence and outcomes of osteosarcoma from our part of the world. We present here our experience of treatment outcomes in adult osteosarcoma patients and correlate our findings with published international data.

Patients and Methods

The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised patient record from 1995 till August 2009. During the period, 188 adult osteosarcoma patients were identified. Only patients who completed the planned treatment were included.

The total dose of chemotherapy for every 3-week cycle consisted of doxorubicin 90mg/m^2, cisplatin 60mg/m^2 and high-dose methotrexate (HDMTX) 8gm/m^2 with folinic acid rescue with variation in schedules in different regimens.

Data was analysed using SPSS version 16. Kaplan Meier survival analysis was used for calculation of event-free survival (EFS) and overall survival (OS) rates. EFS was defined as time interval between the date of last adjuvant treatment till the development of metastasis or local recurrence. OS was defined as time interval between the day of diagnosis and the time of death from any cause.

Results

Of the 74 patients in the study, 58(78%) were in the 18-29 age group and 7 (9.5%) were over 40 years of age with an overall male-to-female ratio of 3:1. The commonest site of disease was femur 30(43%) followed by tibia 27(37%) and fibula 5(7%). Humerus, facial bone and extra-osseous involvement were 3 (4%) for each site. Localised disease (LD) at presentation was found in 63 (85%) patients and metastatic disease (MD) in 11 (15%). The commonest site of metastasis was lungs in 7/11 (64%). The median duration of follow-up was 1.94 years. Eighteen patients underwent primary definitive surgery (PDS) i.e. surgery without any prior chemotherapy. Besides, 51 patients

Table-1: Treatment Outcomes.

	n (%)
Limb amputations	59/66 (89)
Limb salvage	7/66 (10.6)
Histopathological response following NAC¥	
Good	18 (35)
Poor	33 (65)
Good Histopathological response	
HD MTX§	7/20 (35)
Non HD MTX	11/31 (35)

¥ NAC = Neo-adjuvant chemotherapy
§ HDMTX = High-dose Methotrexate.

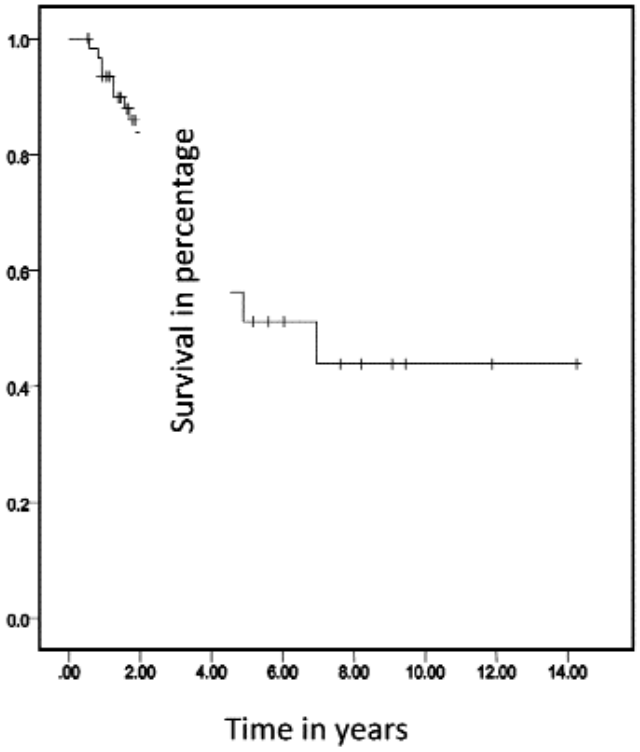

Figure-1: Overall survival of osteosarcoma patients with Localised disease at presentation.

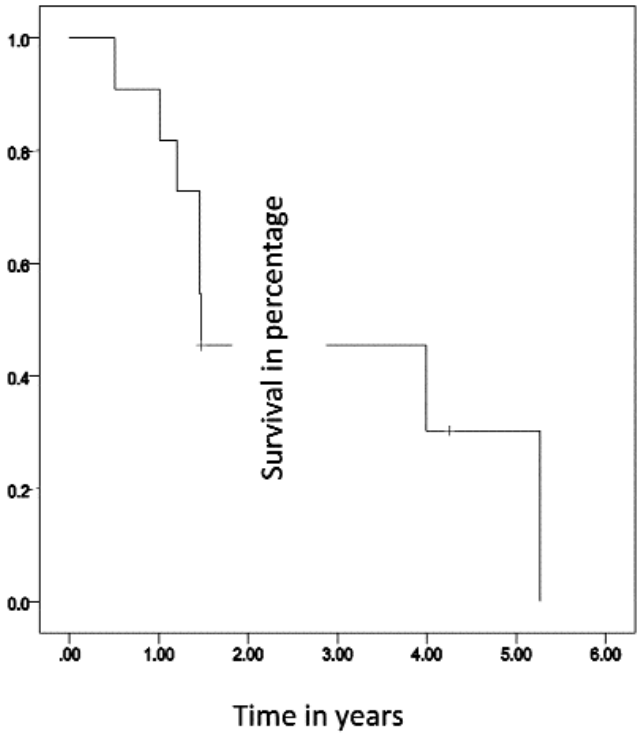

Figure-2: Overall survival of osteosarcoma patients with metastatic disease at initial presentation.

received NAC which was cisplatin and doxorubicin based. HDMTX was part of chemotherapy in 20(39%) of these patients. In all, 66 patients underwent definitive surgery (PDS=18, NAC =48). Three patients opted out of surgery after NAC. Further, 61 patients received AC. This consisted of cisplatin and doxorubicin in 24(39%), cisplatin, doxorubicin and HDMTX in 28(46%) and ifosfamide-based regimen in 9(15%) patients.

Of the 66 patients undergoing definitive surgery, 59(89%) had amputation. Seven limb salvage operations were in the NAC group. Good histopathological response (>90% tumour necrosis) rate in HDMTX containing regimens was 7/20(35%) and non-HDMTX regimens was 11/31(35.4%) with an overall good response rate I 18/51(35%) (Table-1).

Thirty-four (46%) patients are alive to date (28 [82%] without, and 6 [18%] with disease).

Overall survival for all the 74 patients at 2 years, 3years and 5 years was71%, 54% and 35% respectively. Median survival was 3.2 years (95% CI: 2.4 - 4).

For patients with LD at presentation, median EFS was 1.6 years (95% CI: 0.74-2.3) and median OS was 6.9 years (95% CI: 2.6-11.3). Three year and five-year EFS was 30% and 25% and OS was 71% and 50%respectively (Figure-1).

For patients with MD at presentation, median EFS was 0.66 year and median OS was 1.47 years (95% CI: 0.0-3.4). Three-year OS was 45%(Figure 2).

Median OS for patients receiving HDMTX-containing versus non-HDMTX regimens was 1.7 years versus 2.9 years.

Overall, 38 (51%) patients relapsed with lung as the commonest site of relapse 27(71%). Twelve out of 27(44%) patients with lung-only metastases underwent successful metastasectomy. Median OS for patients who underwent pulmonary metastatectomy was 3.2 years (95% CI: 2-4.5) compared to 2.3 years (95% CI: 2-2.5) for patients who did not undergo pulmonary resection. The OS at 2 years and 5 years was 70% and 53%for the pulmonary metastatectomy patients and 65% and 25% respectively for those who did not undergo metastatectomy.

Discussion

In our study of adult osteosarcoma we found majority patients to be in their third decade of life. Only 7 patients presented above 40 years of age and none of them was more than 60 years. We were unable to find the later peak of incidence similar to the epidemiological data from another institute from our country.[10] However, the age and male preponderance correlates with world incidence rates.[11] Most common site of initial disease was lower end of femur and upper end of tibia. Together, this accounted for 79.6% of the cases. Published data also shows propensity of osteosarcoma to involve femur and tibia. The earlier age incidence peak and involvement of long-bone epiphysis of lower limbs support the hypothesis that osteosarcoma develops in the growing bone and also supports the role of hormonal changes during adolescence. Majority of our study patients presented with localised disease. Synchronous pulmonary metastasis constituted 64% of all the metastatic cases at presentation. This is similar to the frequency of metastasis reported in other studies.[12,13]

One-third of the patients underwent PDS which consisted of limb amputations in all cases. This was due to either large ugly looking tumours, or unbearably symptomatic disease (pain, bleeding or resistant infection). Patients who underwent NAC received cisplatin and doxorubicin with 39% also receiving HDMTX. An overall good histopathological response rate was seen in 35% patients with similar response amongst the HDMTX and non-HDMTX regimen. The median overall survival for patients receiving HDMTX vs non-HDMTX chemotherapy also did not differ significantly in our study population, showing no supremacy of HDMTX regimens which is in accordance with the randomised trials in literature.[14,15] Many studies

albiet non-randomised have, however, shown a positive co-relationship between serum levels of methotrexate, tumour response and outcome.[16,17] The response rate not being translated to survival advantage can be multifactorial in our study of adult patients; like difference in tumour biology and MTX pharmacokinetics. To date, a reasonable and appropriate standard of care chemotherapy regimen for newly diagnosed patients with resectable osteosarcoma outside of clinical trials should be HDMTX, doxorubicin and cisplatin, while we await the largest randomised on-going chemotherapy and outcome analysis trial EURAMOS-1 results.

The definitive surgeries in our study mostly consisted of limb disarticulation and limb amputations and less limb conservation. The reason was possible due to consistency in chemotherapy regimens and the expected response or possibly the large size of tumours. More than half of the patients relapsed with lung being the primary site. Successful pulmonary metastatectomies were carried out in 44% patients. Numerous studies have shown clear benefit of pulmonary metastatectomes performed aggressively and repetitively.[15] We found that patients who underwent pulmonary metastatectomy had a better median overall survival. The 3-year survival for patients who did not undergo pulmonary resection was halved. The metastatectomy survival rates in our patients compare well with results from other parts of the world with 2-year and 5-year OS 70% and 30-35%.[13,18]

We found that overall survival for all the patients in our study at 5years was 35%. This is lower than the survival rates from the developed world, but correlates with data from developing countries.[11,19] The 5-year survival rates reported from North America, Europe and Japan for paediatric population fall between 55-75%. Aljubran et al. reported 5-year survival of 66% in the adult population.[12] The reason for low numbers in our study could be a consequence of late presentation, advanced disease, limited access to early diagnosis and appropriate treatment. Also, poor tolerability of aggressive therapeutic approach may have contributed. The survival rates for patients with localised disease though were better than rates for metastatic disease but are lower than reported in literature.[11,12]

The median OS for MD patients was 1.5 years (95% CI: 0.0-3.4). Our 3-year and 5-year survival results for MD at initial presentation were comparable with the published results of previous larger series.[20] Among the MD patients, 64% had lung metastasis. The intended treatment included aggressive surgery combined with multi-agent chemotherapy.

The amount of evidence-based information about adult patients is limited especially from our part of the world. The reason that many patients opted out of treatment was due to the social stigma attached to limb amputation or disarticulation, poor rehabilitation services, limited access to multi-modality treatment and patients were unable to tolerate aggressive chemotherapy regimens.

Conclusion

Adult osteosarcoma treated with cisplatin/doxorubicin-based chemotherapy and surgery has good outcomes. The role of HDMTX in adult osteosarcoma remains uncertain. Survival rates for localised osteosarcoma in our population were comparable with results from developing countries. In our experience a vast majority of patients declined treatment due to fear of limb amputation. Pulmonary metastatectomy improved long-term survival.

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