RESEARCH ARTICLE

Clinicopathologic Features and Prognosis of Osteosarcoma in Turkish Adults

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Abstract

Background: Osteosarcomas are the most common solid malignancies of bone. In the last two decades there have been no concrete developments in their systemic treatment. In this trial we aimed to present our osteosarcoma patient clinical and demographic outcomes. Materials and Methods: Patients treated and followed up for osteosarcoma in Ankara Numune Education and Research Hospital from 2002 to 2012 were reviewed retrospectively. Results: A total of 21 patients (15 male, 6 female) were diagnosed with osteosarcoma. The disease was located at extremities in 76% and in 14% was metastatic at the time of diagnosis. Median disease free survival (DFS) was 36 months in non-metastatic patients and median progression free survival (PFS) was 2 months in metastatic patients (p<0.0001). Median overall survival (OS) was 80 months and 4 months, respectively (p=0.012). There were no survival differences in terms of presentation with pathological fracture, tumor size, tumor grade, alkaline phosphatase and lactate dehydrogenase level and type of chemotherapy regimen. Conclusions: Tumor site and stages are the most important prognostic factors for osteosarcoma. Extremity primary tumors have beter survival rates than non-extremity tumors. As a result of the use of effective chemotherapy the long term survival rates have improved from 10-20% to 60-70% in the last decades but we need more active agents, especially for metastatic cases.

Keywords: Osteosarcoma - treatment - prognosis - adults

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Introduction

Osteosarcomas are derived from primitive mesenchymal cells of bone and rarely soft tissue (Ritter and Bielack 2010). It is the most common solid malignancy of bone. Its incidence is 2-3 per 106 peoople in general but 8-11 per 106 people aged 15-19 years. Male female ratio is 1.4 (Stiller et al., 2006; Qureshi et al., 2010). In many patients, osteosarcomas take origin from distal femur, proximal tibia and proximal humerus and 10% osteosarcoma develop in the axial skeleton (Bielack et al., 2002). The most common symptoms are local pain, swelling and limitation of joint movement. In some cases pathological fracture may be the first sign of disease.

Plain radiographs are usefull to assess the changes at the bone. But osteosarcomas often have soft tissue component and magnetic resonance imaging (MRI) is more suitable to assess soft tissue component. MRI should include whole affected bone. A thorax computed tomography is also essential. Approximately 15% of patients are metastatic. The most common metastatic sites are lung and to a lesser extend bone (Ritter and Bielack, 2010). In non-metastatic patients the cornerstone of the treatment is surgery. But 80-90% of patients treated with only surgery develop metastasis. With the use of preoperative and postoperative chemotherapy it is possible to achive cure in two-thirds of patients (Kudawara et al., 2013). In metastatic patients the choice of treatment is chemotherapy. Survival rates range from 10 to 50%. But in a minority of patients with limited lung metastasis it is possible to achieve long survival rates with chemotherapy and surgery (Kager et al., 2003). The most active agents for osteosarcoma are doxorubicin, cisplatin, methotrexate and ifosfamid (Anninga et al., 2011).

Unfortunately, in the last two decades there have been no development in the systemic treatment of osteosarcoma. Because of the rarity of the disease it is very very difficult to activate a clinical trial without participation of multi centers. In this trial we aimed to present our osteosarcoma patient's clinical and demographic outcomes.

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Materials and Methods

Patients included in this study were those treated and followed up for osteosarcoma in Ankara Numune Education and Research Hospital from 2002 to 2012. The patients's data reviewed retrospectively. The patient's gender, ages, tumor localisations, dimensions and grades, pathological fractur status, primary treatment modality, if admitted response to preoperative chemotherapy, type of surgery and adverse events related with chemotherapy had recorded. The patients extremity, torax and abdominal imagings had done and stages determined. Also patient's hematological parametres, liver and kidney function tests and also alkaline phosphatase and lactate dehydrogenase values had recorded. According to the WHO criteria hemoglobin levels below 13 g/dl and 12 g/dl in males and females accepted anemia, respectively.

Statistical analyses were performed by using SPSS for Windows version 13.0 (SPSS, Chicago, IL) Baseline characteristics of groups were compared by X^2 tests (for categorical variables) or two sample t tests (for continuous variables). Tumors with missing values were omitted from the analyses. Kaplan-Meier survival analysis was carried out for disease-free survival (DFS) and overall survival (OS). The log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided P values of <0.05 were considered statistically significant.

Results

A total of 21 patients had diagnosed with osteosarcoma in our center between 2002 and 2012. Patient's characteristics and hematologic and biochemical parameters are given in Tables 1 and 2.

There was not signicant difference in terms of tumor localization and stage at time of diagnosis. All of 3 metastatic patients had presented with pathological fracture, whereas only three of the 18 non-metastatic patients had presented with pathological fracture (p=0.003). The pathological tumor grade was specified in 14 patients. Two patients had low grade, two patients had intermediate grade and 10 patients had high grade tumor. Both of the metastatic patients had high grade and >60mm tumors whereas the tumor was >60mm in 59% (n=10) of non-metastatic patients.

Two metastatic patients had treated with chemotherapy. Both of them received cisplatin and adriamycin (AC). One of the non-metastatic patients had treated with only chemotherapy and 1 patient had treated with only radiotherapy depending on patient's preference and 16 patients had treated with surgery. Six patients (50%) had undergone limp sparing surgery. Ten of non-motastatic patients (55%) had received preoperative chemotherapy and 15 patients (83%) had received postoperative chemotherapy. Five patients had received ifosfamide, mesna and adriamycin (IMA), 8 patients had received AC and 4 patients had received IMA and AC with alternating cycles. Four patients also received pre/postoperative methotrexate.

The median follow up period was 80 months (4-126 months). During the follow up period 57% of non-metastatic patients (n=8) had relapsed and 100% of metastatic patients (n=2) had progressed. Eight of these 10 patients had treated with chemotherapy. We had gained partial remission in 3, stable disease in 2 and progressive disease in 3 patients.

Table 1. Patient's Characteristics

		n	(%)
Gender	Male	15	(71%)
	Female	6	(29%)
Age (years)		27	(16-68)
Localization	Extremity/upper	5	(24%)
	Extremity/lower	11	(52%)
	Head & neck	4	(19%)
	Vertebra	1	(5%)
Stage	Non-metastatic	18	(86%)
	Metastatic	3	(14%)

Table 2: Patient's Complete Blood Count and Biochemical Parameters

	Non-metastatic	Metastatic	p
Wbc ($x10^3/mm^3$)	7.85±2.6	6±0.3	>0.05
Hgb (g/dl)	12.1±2	13.5±1.4	
Creatinin (mg/dl)	0.75±0.1	0.8±0.1	
LDH (U/L)	242±353	469±366	
ALP (U/L)	110±121	162±42	
AST (U/L)	19±8.4	23±14	
ALT (U/L)	16.5±10	24±29	
Calcium (mg/dl)	9.1±0.4	9.5±0.6	

Wbc: white blood cell; Hgb: hemoglobin; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Median disease free survival (DFS) was 36 months in non-metastatic patients and median progression free survival (PFS) was 2 months in metastatic patients (p<0.0001). There was not a DFS or PFS difference between male and female patients and between patients under 30 years and older than 30 years. DFS was 75 months in non-metastatic patients whose tumor was located in extremities and 15 months in non-extremity primary tumors (p=0.014). In non-metastatic patients the DFS was 36 months in high grade tumors and 10 year DFS was 66% in low and intermediate tumors (p>0.05). There was not a DFS difference between non-metastatic patients who had received neoadjuvant chemotherapy or not and had received methotrexate or not.

Median overall survival (OS) was 80 months in non-metastatic patients and 4 months in metastatic patients (p=0.012). There was not an OS difference in male and female patients and between patients under 30 years and older than 30 years. The OS was 80 months in extremity primary tumors and 24 months in non-extremity primary tumors in non-metastatic patients (p=0.007). In non-metastatic patients the OS was 80 months who had received neoadjuvant chemotherapy and 24 months who had not (p=0.032). There was not an OS difference between low, intermediate and high grade tumors and between patients who had received methotrexate or not.

There was not a DFS/PFS/OS difference in terms of presentation with pathological fracture, tumor

size, tumor grade, alkaline phosphatase and lactate dehydrogenaselevel and type of chemotherapy regimens.

Discussion

Although osteosarcoma is an uncommon disease it is the most common malignancy of bone and the disease is slightly more common in males (Stiller et al., 2001; Stiller et al., 2006; Sampo et al., 2011). Between 2002 and 2012 a total of 21 patients had diagnosed and treated with osteosarcoma and male female ratio was 2.5 at our clinic. In United States and Europe the disease is most common in 2nd decade and has a small peak in 7th decade (Ritter and Bielack, 2010; Anninga et al., 2011). Because of only adult patients have treated in our clinic all of our patients were older than 16 years old. But only one of the patients was older than 60 and one older than 50. At our clinic the median age was 27 and 66% of patients were under age 30. Also, in the studies of Arslan et al and Arikan et al, the the peak incidence of osteosarcoma patients was after 20 years in Turkey (Arikan et al., 2007; Arslan et al., 2011). This may be due to different biology of osteosarcoma in different regions.

In the current study, compatible with the information in the literature the most common sites were lower extremities and upper extremities and 14% of patients were metastatic at the time diagnosis (Bielack et al., 2002; Mialou et al., 2005). In our patients pathological fracture was more common in metastatic group. The clinical importance of presentation with pathological fracture is nor clear. Some authors states that pathological fracture is related with worsen survival outcomes whereas others not (Scully et al., 2002; Xie et al., 2012). We did not determine an overall or progression free survival difference in term of presentation with pathological fracture.

The present study had showed that the tumor site is an important prognostic factor. Extremity primary tumors have beter survival rates than non-extremity tumors. In the study of Bielack et al the 5 year OS was 81% in extremity primary tumors (Bielack et al., 2002). The 5 year OS for pelvic osteosarcomas was 27% at the study of Kawai et al (Kawai et al., 1998). Shives et al and Ozaki et al had found median OS under 2 years for spinal osteosarcomas (Shives et al., 1986; Ozaki et al., 2002). In our study the 5 year OS for extremity primary tumors was 100% and median OS was 2 years for non extremity tumors. Another remarkable result from the present study was, patients who had received neoadjuvant chemotherapy had better OS rates.

The survival of patients with osteosarcoma has improved dramatically over the past 30 years. Previously 80 to 90 percent of osteosarcoma patients developed metastases despite achieving local tumor control, and died of their disease. As a result of the use of effective chemotherapy the long term survival rates had improved from 10-20% to 60-70% (Eilber et al., 1987; Bielack et al., 2009; Diao et al., 2014). In our patients the 5 year survival rate for non-metastatic patients was 83%. The DFS and OS were 36 and 80 months for non-metastatic patients. Despite these better survival rates for non-metastatic patients, metastatic patient's survival rates were unsatisfactory. The 5 year OS for patients who had metastasis during follow up is 30-50% and 0% for patients who had metastasis at initial diagnosis (Clark et al., 2008; Ritter and Bielack, 2010; He et al., 2013). In the study of Meyers et al the 2 year OS for metastatic patients were 11% (Meyers et al., 1993). In the present study the PFS and OS for metastatic patients were 2 and 4 months, respectively. The relative better outcomes for metastatic patients at other studies are due to patients who has only lung metastasis and underwent curative metastasectomy (Kager et al., 2003). Both of our 2 metastatic patients has multipl metastasis and they were not surgical candidates. Based on these result it can be conclueded that chemotherapy in metastatic setting is not as effective as in adjuvant and neoadjuvant setting.

Alhought, osteosarcoma is more common in teenagers, it may be seen in every age population. The most important prognostic factors are stage and tumor site. Presentation with pathological fracture, lactate dehydrogenase, alkaline phosphatase levels did not have prognostic importance, in this study. The mainstay of treatment for non-metastatic patients is surgery and perioperative chemotherapy is very important for long survival rates, also. Both AC and IMA are very active regimens in the adjuvant setting but we need more active agents for metastatic patients.

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