Neoadjuvant and Adjuvant Chemotherapy in Osteosarcoma (The Experience of HORC in the Shariati Hospital)

Alimoghadam K., Ghavamzadeh A., Jafari M., Sami Hagialilo S., Jahani M., khodabandeh A., Eghbal L., Gholibekian S.

Hematology- Oncology and Bone Marrow Transplant Department, Shariati Hospital, Tehran University of Medical Sciences, Tehran, IRAN

Background: Osteosarcoma is the most common bone sarcoma, and the third most common malignancy in children and adolescents. Before 1970, amputation was the sole treatment. Eighty percent of patients died from metastatic diseases, most commonly in the lungs. Over the past three decades, effective neoadjuvant (preoperative) and adjuvant (postoperative) chemotherapy protocols have improved the ability to perform limb salvage resections, disease free survival and overall survival rates.

Patients and Methods: The study was conducted on 28 patients (15 male and 13 female) whose diagnoses were confirmed by excisional biopsy without any proof of metastasis in clinical and radiological assessments from September 2001 to November 2002. All patients were treated with three-drug regimen consisting of Adriamycin, Ifosfamide and Cisplatin. The neoadjuvant chemotherapy was administered in three courses. The first course, Ifosfamide (2gr/IV) and Adriamycin (75mg/m², IV infusion) were given on the first day and Ifosfamide (1.5 gr/m² by continuous infusion) alone for 6 days. The second course consisted of Adriamycin (75mg/m², IV infusion) and Cisplatin (100mg/m², IV infusion) for one day. The third course was the same as the first. After surgery, all patients received adjuvant therapy similar to the neoadjuvant protocol mentioned above. Limb salvage was the most common surgical method. The treatment outcome particularly depended on the percentage of tumor necrosis. Overall and disease-free survival were also measured.

Results: According to the tumor necrosis percentage, the tumor response to chemotherapy was classified from good to poor response. In this study, 63.6% of patients showed good response and 36.4% indicated poor or no response to chemotherapy. The tumor necrosis percentage was significantly correlated with age≤ 20 years (P= 0.01), tumor size ≤84 cm³ (P= 0.03) and the site of tumors in femurs (P= 0.03). The average follow-up time was 132 days, ranging from 15 to 618 days. The first year survival rate was 100%, and the disease-free survival (DFS) was 70.8% for the same time period. Disease-free survival was significantly correlated with the chemotherapy response (P= 0.03), which was 100% in the good response group in the first year.

Conclusion: Although we had utilized bone grafts for substantially resected bones, local relapses were remarkably low (2 cases), so we suggest that this surgical method can be a proper alternative treatment for different types of expensive prosthesis in countries with low socioeconomic status.

Keywords: Osteosarcoma, Neoadjuvant chemotherapy

Introduction:

Osteosarcoma is the most common bone sarcoma, and the third most common malignancy in children and adolescents. Frequently, the origin of the tumor is the distal end of long bones in metaphyseal regions, although the tumor can develop in any bone.[1] Depending on the site where the tumor occurs, osteosarcoma may be originated primarily, which occurs in normal bones (about 95% cases) or secondarily, which occurs in bones that have already some how changed (as result of radiation, infection, Paget's disease, etc). Most osteosarcomas are classified as conventional, high-grade tumors.[1, 3]

Before 1970, amputation was the only treatment for a high-grade osteosarcoma. Eighty percent of patients died from metastatic disease, mainly involving lungs.[2] Over the past three decades, a development of surgical techniques improved imaging modalities towards a more accurate distinction of tumor extent, and effective chemotherapy has made limb salvage procedures a safe alternative to amputation, and led to an increase in disease-free and overall survival rates.[1,6] Associated chemotherapy (adjuvant or neoadjuvant) denotes the association of systemic pharmacological therapy in treatment of tumors that, although appearing to still be localized at the time of diagnosis, have a high probability of having already given systemic micrometastases.[3]

Today, the most effective chemotherapy agents currently in use include: high-dose Methotrexate, Doxorubicin, Cisplatin and Ifosfamide.[6] Also, 90 to 95% of patients with osteosarcoma can be treated with limb salvage surgery and 60 to 80% of patients with localized disease are long term survivors. Despite the success of these combined treatments, metastases still develop in approximately 30-40% of cases.[1] After relapse, about 80% of these patients will die as a result of tumor relapse, and only 20% can be cured by a second line treatment (metastasectomy with or without further chemotherapy). Therefore, the identification of relapse risk factors in patients treated with neoadjuvant

and adjuvant chemotherapy, is of major importance in the development of treatment.[4,8]

Materials and Methods:

Patients: 31 patients with osteosarcoma were enrolled in a study at the Hematology-Oncology and Bone Marrow Transplantation Research Center of the Shariati Hospital (HORC), from September 2001 to November 2002. Three patients who demonstrated metastases at the time of admission were excluded. The remaining 28 patients had the following characteristics:
1- History of other tumors was positive in four patients. One had a history of a malignant tumor (retinoblastoma) and the others had benign tumors. Also, one patient suffered from Werner's syndrome.
2- Three patients had a positive history of cancer in their family. (osteosarcoma, breast cancer and leukemia)
3- No previous treatments had been given to patients.

Preoperative evaluation and chemotherapy: The diagnosis of osteosarcoma, established by clinical and radiological findings, was always confirmed by histology of tumor tissue obtained from an open or needle biopsy as well as on the resected specimens. The primary tumor was evaluated by standard radiography, CT scan and MRI. Bone metastases were evaluated by whole body scans and chest x-ray or lungs CT scan. Serum alkaline phosphatase activity was measured in international unit (IU) with optimized kinetic method on admission. The neoadjuvant chemotherapy was administered in three courses including Ifosfamide (2gm/day) and Adriamycin (75mg/m²/day), then Ifosfamide (1.5gr/m², for 6 days) in the first course. The second course consisted of Adriamycin (75mg/m²/day) and Cisplatin (100mg/m²/day), and the third course was the same as the first one. A three-course adjuvant therapy, similar to the neoadjuvant protocol, was administered after the operation.
Surgery: Limb-salvage was the main surgical method, using bone graft replacement. Three patients, with poor response to chemotherapyy, underwent ablative surgery.
Follow-up: During postoperative chemotherapy, patients were evaluated by serial tumor site and chest X-rays. Additional evaluations were made when indicated by clinical conditions. After completion of chemotherapy, patients were followed up with the same examination at 2-month intervals.
Statistical considerations: The main aims of this study was to determine the efficiency of the protocol, plus overall and disease free survival. Also, the correlation between pretreatment serum alkaline phosphatase and the prognosis was evaluated.

Results:

In the present study, the gender pattern of patients included fifteen males and thirteen females with a median age of 17 years (from 13 to 40). Twenty patients were under 20 years old and others over 20. The most common site of tumors included the distal of femur (16 cases) and tibia (7 cases). Other involved sites included humorous (2 cases), fibula (1 case) and jaw (2 cases). Pain and swelling were considered common clinical signs of tumor. The major histological patterns of tumors consisted of osteoblastic and chondroblastic forms (13 and 7 cases). Fibroblastic and telangiectatic histological patterns were seen in one and two patients, respectively. Five missing data existed in this category. The major chemotherapy side effects consisted of nausea, vomiting (15 cases) and bone marrow suppression (5 cases). No side effects were registered in three patients. Chronic heart failure (2 cases) and hemorrhagic cystitis (1 case) were other complications that appeared after chemotherapy.

Table 1: Correlation of Tumor necrosis percentage (TNP) with several variables.

Variable	No. of patient	No.of TNP**	P-Value
Gender			
Male	15	10	ns
Female	13	12	
Age			
≤20yr	20	17	0.01
>20yr	8	5	
Site			
Femur	16	14	0.03
Other site	12	8	
Size			
≤84cm²	12	11	
>84cm²	5	3	0.03
Undetermined	11	8	
Histology			
Osteoblastic	13	11	
Other	10	7	ns
Undetermined	5	4	
DFS			
Determined	24	19	0.03
Undetermined	4	3	

**** Data missing in 6 patients.**

Tumor response to chemotherapy was another item, which was assessed by percentage of necrosis on biopsy after surgery. The chemotherapy response was classified into good, moderate and poor or no response. In our study, 63.6% of patients had a good response, 18.2% moderate and 18.2% had poor or no response to chemotherapy (Table I). Patients' response was significantly correlated with age (P= 0.01), tumor size (P= 0.03), tumor site (P= 0.03), and disease free survival (P= 0.03). No significant relation was found between tumor necrosis percentage and other variables listed in Table I.
On the other hand, the pretreatment serum alkaline phosphatase (SAP) was examined to evaluate whether the enzyme level had a clinical role in predicting the

the course of the disease. In our study, twelve patients were within the normal SAP range and thirteen exceeded the normal range. There were three missing data. No correlations were found between SAP variables versus other variables, i.e., gender, age, site, size, histological pattern of tumors, and chemotherapy response.

The determination of disease-free survival and overall survival was another aspect of our study. Disease-free survival (DFS) was defined as the time beginning from surgery until the last follow-up or the time of metastases or local recurrence. After one year of follow up, disease free survival based on the Kaplan-Mayer analysis was 70.8 % ± 0.16. The median time of DFS was 132 days (ranging from 15 to 618 days). Four relapses occured. Metastases to other organs were reported in three patients (two cases with lung metastasis and one patient with metastases to sphenoid sinuses) and one case with regional relapse in surgical site.

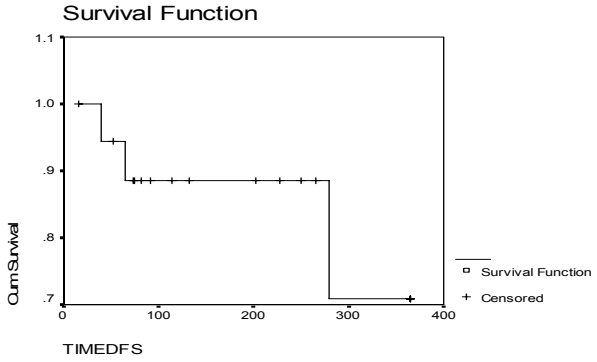

Figure 1: One year disease-free survival

The DFS was longer in females (87.5% in females to 59.2% in males), age under 20 (82.5% in under 20 years to 50% in over) and the tumor size over 84cm^3 (100% in over 84cm^3 to 60% in under 84cm^3). Also it was longer in other bones (87.5% in other bones to 77.7% in femur origin), the limb-salvage surgery (81.8% in limb-salvage to 66.6% in other surgical methods), normal SAP range (87.5% in normal SAP to 57.4% in high SAP) and good response to chemotherapy (100% in good to 60% in poor response). The only significant correlation was seen between DFS and chemotherapy response (P= 0.03). The P-value in other variables was not significant.

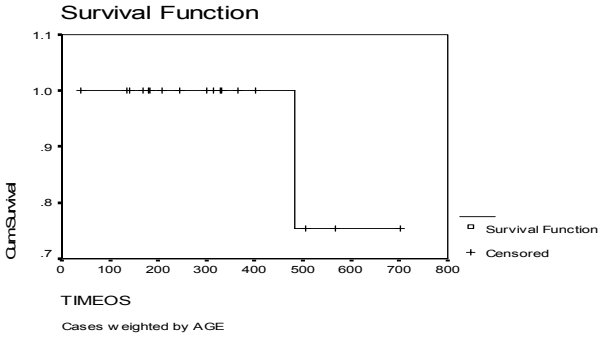

Figure 2: Overall survival

The overall survival (OS) was defined as the period from the beginning of treatment to the last follow-up or death. The one-year overall survival in our patients was 100% with the median time 329 days (ranging from 40 to 703 days). The OS was longer in females (100% in females to 75% in males), age over 20 years (100% in over 20 yr to 66% in under 20 yr) and the tumor size over 84cm^3 (100% in over 84cm^3 to 70 % in under 84cm^3). Also, it was longer in other bones (100 % in other bones to 80% in the femur origin), normal SAP range (100% in normal SAP to 50% in high SAP) and good response to chemotherapy (100% in good to 66% in poor response). Overall survival was 66.6% in limb-salvage and 100% in other kinds of surgery. There was no correlation between the above variables and overall survival.

Conclusion:

Our report is a preliminary report of results of chemotherapy and surgery in osteogenic sarcoma. In several studies, it was reported that combination of high dose Ifosfamide, Cisplatinum, Adriamycine and high dose Methotrexate can lead to about 33-80%[2,7] good response in patients after neoadjuvant chemotherapy and in good responders a longer DFS was expected.[2,4,5,9,10,11,12] Due to the small number of studied patients, our findings can not be compared with other large scale surveys; but a good response rate in our study (63.6%) is comparable to other studies.[2,12] Also, we cannot compare our DFS results due to the short period follow up of patients.

Although we have used bone grafts for substantially resected bones, the local relapses rate in our study was actually low (2 cases), so we suggest this surgical method in countries with low socioeconomic status as a suitable alternative treatment to different types of expensive prosthesis. On the other hand, the outcome data suggests that lack of a near complete response to preoperative chemotherapy reflects inherent biologic resistance to chemotherapy and hence, a poor prognosis.

References:

1- James C. Witting, Jacob Bickels, Dennis Priebat, *et al*. Osteosarcma: A multidisciplinary approach to diagnosis and treatment. *Am Fam Physician Mar 15, 2002; 65:1123-32, 1135-6. Copyright© 2002 American Academy of Family Physicians*.

2- Patel SJ, Lynch JW Jr, Johnson T, Carroll RR, *et al*. Dose-intense ifosfamide/doxorubicin/cisplatin based chemotherapy for osteosarcoma in adults. *Am J Clin Oncol 2002 Oct*; 25(5):489-95.

3- Bacci G, Lari S, *et al*. Adjuvant and neoadjuvant chemotherapy in osteosarcoma Chir Organi Mov, 2001 Oct-Dec.

4- Bacci G, Longhi A, Ferrari S, *et al*. Prognostic significance of serum alkaline phosphatase in osteosarcoma of the extremity treated with neoadjuvant

chemotherapy: recent experience at Rizzoli Institute. *Oncol Rep 2002 Jan-Feb*; 9(1):171-5.
5- Bacci G, Ferrari S, Longhi A, *et al*. Pattern of relapse in patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy. *Eur J Cancer 2001 Jan;* 37(1):32-8.
6- Ferguson WS, Goorin AM. Current treatment of osteosarcoma. *Cancer Invest 2001;* 19(3):292-315
7- Bacci G, Ferrari S, Bertoni F, Picci, *et al*. Histologic response of high-grade nonmetastatic osteosarcoma of the extremity to chemotherapy. *Clin Orthop 2001 May ;*(386):186-96.
8- Ferrari S, Bertoni F, Mercuri M, *et al*. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: an analysis of 300 patients treated at the Rizzoli Institute. *Ann Oncol 2001 Aug;* 12(8):1145-50.
9- Wozniak W, Rychlowska M, *et al*. Evaluation of indications and the perspectives of limb salvage surgery in malignant bone tumours in children and youth. *Med Wieku Rozwoj 2000 Apr-Jun;*4(2 Suppl 2):85-93.
10- Cai Y, Niu X, Zhang Q, *et al.* Long-term results of combined therapy for primary osteosarcoma in extremities in China. *Zhonghua Wai Ke Za Zhi 2000 May;38(5):329-31.*
11- Renard AJ, Veth RP, Schreuder HW, *et al*. Osteosarcoma: oncologic and functional results. *J Surg Oncol 1999 Nov; 72(3):124-9*
12- Robert L Souhami, Alan W Craft, Jan W van der Eijken, *et al*. Randomised trial of two regimen of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet. 1997 Sep 27;350(9082):911-7*