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Clinical Features, Prognostic Factors and Treatment Outcome of Chondroblastic Osteosarcoma: A Single-Center Experience

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Abstract

Objective: Chondroblastic osteosarcoma is an aggressive bone cancer with poor outcome accounting for 25% of cases of conventional osteosarcoma. The aim of our study was to assess the clinico-epidemiological profile, prognostic factors, and treatment outcome of chondroblastic osteosarcoma.

Methods: A monocentric retrospective study was conducted between 1982 and 2020. Data of chondroblastic osteosarcoma patients treated in Salah Azaïz Institute were collected. Patient's treatment variables, prognostic factors and and treatment outcome were assessed.

Results: Thirty patients were included. Most of them (n=24) were younger than 25 years. Femur (n=15) and tibia (n=8) were the most common sites involved. Twenty patients had localized disease and 10 patients had metastatic disease on presentation. Neoadjuvant chemotherapy was performed in 23 patients. They received combination regimen of methotrexate, adrimaycin and cisplatin (MAP) (44%), methotrexate, etoposide and ifosfamide (30%), combined doxorubicin-ifosfamide-cisplatin (API) and doxorubicin-ifosfamide (AI) (22%), etoposide, ifosfamide and cisplatin (VIP) (4%). 16% of patients had partial response, 63% a clinical progression and 21% patients a stable disease. Surgery was performed in 22 patients. Of 16 patients operated, 4 (25%) were good responders while 12 (75%) were poor responders. For patients with metastatic disease, only one achieved complete remission. Six patients progressed after treatment and two died. For patients with localized osteosarcoma, 6 patients had local recurrence and 6 patients had distant metastases. Median overall survival was 35 months. Overall survival at 2 years was 43%. Median disease free survival was 12 months. Disease free survival at 2 years was 21%. The absence of clinical response after neoadjuvant chemotherapy and age> 25 years were prognostic factor influencing disease-free-survival (p=0.025 and p=0.012, respectively).

Conclusion: Chondroblastic osteosarcoma is an aggressive tumor with a tendency for local recurrence and distant metastasis. Younger onset age and response to neoadjuvant chemotherapy can predict better disease free survival.

Keywords: Chondroblastic • Osteosarcoma • Chemotherapy • Prognostic

Introduction

Osteosarcoma is a highly malignant bone tumor. It is the most common primary malignant bone cancer accounting for 15%-35% of all primary malignant bone neoplasms [1]. It has a predilection for adolescents and young adults. Osteosarcoma can be very aggressive with rapid growth and early metastases to the lungs and bones. Chondroblastic osteosarcoma is one of the most common subtypes of osteosarcomas with percentage of 11% to 50%.

It is usually diagnosed in young adults with a peak at about twenty years old [2]. The symptoms depend on location and size of the tumor. The presentation can vary from pauci-symptomatic forms to severe pain, swelling, deformity and loss of function.

The histopathological diagnosis is based on the predominance of a chondroid matrix formed in the midst of neoplastic cells. Treatment regimens for chondroblastic osteosarcoma are the same as those used for conventional osteosarcoma. Neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy remain the mainstay of treatment for this tumor. Chondroblastic osteosarcoma has often a poor response to chemotherapy and an unfavorable prognosis compared to other osteosarcoma histological types [3]. In the literature, few studies have assessed the clinical, therapeutic and prognostic factors of chondroblastic osteosarcoma.

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The aim of our study was to assess the clinic-epidemiological profile, prognostic factors, and treatment outcome of chondroblastic osteosarcoma.

Materials and Methods

Study design

A retrospective study including all consecutive patients with chondroblastic osteosarcoma was performed at a tertiary-level hospital over a period of 38 years between 1982 and 2020. This study has been approved by the institution's Ethics Committee. Consent to participate was waivered to the retrospective nature of the study. Data were collected and handled anonymously. All patients included should have underwent a biopsy (core needle or surgical) and histologic classification was established according to the World Health Organization classification of 2013. For patients treated before 2013, histopathologic slides were reviewed according to the new classification.

Data collection

Data extracted as part of this retrospective analysis included age at diagnosis, gender, medical history, the diagnostic delay, date of diagnosis, tumor size, primary site, surgical margins, chemotherapy regimen, response rate, metastasis at diagnosis, treatment strategies, recurrence rate, date of progression, time to progression, date of last follow-up, and survival status.

Margin was classified as gross positive (R2), microscopic positive (R1), or negative (R0).

Neoadjuvant chemotherapy was based on Rosen T8-T12 regimens including (methotrexate, cisplatin, doxorubicin, bleomycin, dactinomycin, cyclophosphamide), API/AI regimens (cyclophosphamide, doxorubicin, ifosfamide) or etoposide ifosfamide, methotrexate regimen, depending on the age of the patient. Patients older than 25 years received API/AI chemotherapy.

Patients aged under 18 years were treated with methotrexate-based regimens. Intermediate aged patients (18–25 years) were treated with Methotrexate regimen in most cases.

Surgery (amputation or limb sparing surgery) was performed in an expert center. Adjuvant chemotherapy was performed according to the tumor necrosis rate assessed by Huvos. Ninety percent of tumor necrosis was the threshold for a good response.

Patients received regular follow-ups consisting of clinical examination and a yearly chest computed tomography (CT). They were checked every 3 months during the 2 first years and then, every 6 months during 3 years. For the five following years, it was scheduled yearly.

Statistical analysis

The data were analyzed on the Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS, Armonk, NY, USA). Results were expressed as mean ± standard deviation. Univariate comparisons between groups were performed using chi-squared tests for dichotomous variables or Fisher's test when appropriate. For continuous variables, independent samples t-tests were used. $P<0.05$ was considered to be significant. Cumulative event rates were calculated using the method of Kaplan–Meier. Survival curves were compared using the log-rank test. Recurrence-free survival was determined as the time from diagnosis to either histology-proven or radiologic evidence of disease recurrence. Overall survival for patients who died was determined as the time from the date of diagnosis to the date of death. For patients who were still alive, it was determined as the time from the date of diagnosis to the date of the last follow-up. Due to the small number of patients, the multivariate study was not statistically possible.

Results

Thirty patients (15 males and 15 females) were included in our study. The mean age was 21 years (range, 8-62 years). One patient had history of hereditary retinoblastoma and had radiation therapy. The most common presenting complaint were pain (n=30) and swelling (n=25). One patient had a fracture at diagnosis. Nine patients had history of trauma. Physical examination revealed palpable mass (n=24), localized warmth/erythema (n=8) and restricted joint motion (n=15). One patient had spinal cord compression. The primary tumor was located in the lower limbs in 23 patients: in the femur in 15 patients and in the tibia in 8 patients. The lesion was located in the humerus (n=1), the scapula (n=1), the axial skeleton (n=4) and the mandible (n=1). Characteristics of the 30 patients included in our study are detailed in Table 1. Local staging of osteosarcoma was assessed by X-ray, Magnetic Resonance Imaging (MRI) and/or bone Computed tomography (CT). For distant staging, chest X-ray, chest CT and bone scintigraphy were performed. Twenty patients had localized disease and 10 patients had metastatic disease on presentation.

In imaging, intra-articular extension was found in 31% of our patients, neural or vascular invasion in 21% and soft tissue involvement in 62% of them. Two patients had skip metastasis. Seven patients had lung metastases on presentation, one patient had bone metastases and 2 patients had both lung and bones metastases. One patient with metastatic disease was lost to follow-up before any treatment.

Neoadjuvant chemotherapy was performed in 23 patients and 6 patients underwent immediate surgery. Seventeen patients received high-dose methotrexate (MTX) regimens (7 had MTX-etoposide-ifosfamide, 10 had MAP), 5 patients had combined API/AI courses and one patient received VIP regimen. 16% of patients had partial clinical response, 63% of patients had clinical progression and 21% patients had stable disease. Surgery was performed in 22 patients: 16 had neoadjuvant chemotherapy followed by surgery and 6 had immediate surgery. Limb salvage surgery was performed in 12 patients while 10 patients had amputation. Complete R0 resection was achieved in 86% of patients while 5% had R2 resection. The type of resection was not specified in 9% of patients. On histopathological examination of specimens, mean percentage of viable tumor was 37% (range 3%-67%). Of 16 patients, 4 patients (25%) were good responders while 12 patients (75%) were poor responders. Adjuvant chemotherapy was performed in 16 patients. Seven patients had combined API/AI courses, 6 had high-dose MTX regimens and 3 had high-dose methotrexate (MTX) regimens and 3 had VIP regimen. Two patients had adjuvant radiation therapy. shows the treatment outcome of patients with localized and metastatic osteosarcoma (Table 2).

Table 1. Characteristics of patients.

Treatment	Frequency	%
Sex		
Male	15	50
Female	15	50
Mean Age=21 years		
History of a hereditary retinoblastoma	1	3
History of radiation therapy	1	3
Presenting symptoms		
Pain	30	100
Swelling	25	83
Fracture	1	3
Trauma	9	30
Physical examination		
Palpable mass	24	80
localized warmth/erythema	8	27
restricted joint motion	15	50
spinal cord compression	1	3
Location of primary tumor		
Femur	15	50
Tibia	8	27
Humerus	1	3
Scapula	1	3
Axial skeleton	4	14
Mandible	1	3
Side		
Right	12	41
Left	17	59
Extension		
Intra-articular	9	31
Neural/vascular	6	21
Soft tissue	18	62
Stage		
Localized	20	67
Metastatic	10	33
Metastases		
Lung	7	70
Bone	1	10
Lung and bone	2	20

For patients with metastatic disease (n=10), only one had achieved complete remission. Six patients had progressive disease after treatment and two have died. For patients with localized osteosarcoma, 6 patients had local recurrence and 6 patients had distant metastases. The most common site for distant metastasis was lung (n=6). One patient underwent surgery, 4 underwent chemotherapy and one patient underwent both surgery and chemotherapy followed by radiation therapy for local recurrence. For patients with distant recurrence, 3 had chemotherapy, one patient had lung metastasectomy and 2 patients had both surgery and chemotherapy. At a mean follow-up of 20 months, 18 patients were alive (13 had progressive disease and 5 had complete remission), 7 patients had died and 5 patients were lost to follow-up. Median overall survival (OS) was 35 months (Figure 1). OS at 2 years was 43%. Median disease free survival (DFS) was 12 months (Figure 2). DFS at 2 years was 21%.

The mean of OS in patients was 67 months and DFS was 26 months

Table 2. Treatment outcome of patients with localized and metastatic osteosarcoma.

	Localized	Metastatic
Neoadjuvant chemotherapy	14	9
Neoadjuvant chemotherapy regimen	MAP (n=7)	MAP (n=3)
	MTX-VP16-ifosfamide (n=4)	MTX-VP16-ifosfamide (n=3)
	API/AI (n=3)	API/AI (n=2)
		VIP (n=1)
Immediate surgery	6	0
Surgery after neoadjuvant chemotherapy	11	5
histologic response	Good responders (n=1)	Good responders (n=3)
	Poor responders (n=10)	Poor responders (n=2)
	13	3
Adjuvant chemotherapy	API/AI (n=6)	MAP (n=2)
Adjuvant chemotherapy regimen	MAP (n=1)	AP (n=1)
	MTX-doxorubicin-cyclophosphamide-vincristine (n=1)	
	MTX-VP16-ifosfamide (n=2)	
	VIP (n=3)	

Note: MAP: MTX-Doxorubicne-Cisplatin; VIP: Etoposide, Ifosfamide, Cisplatin; API: Doxorubicin-Ifosfamide-Cisplatin; AI: Doxorubicin-Ifosfamide.

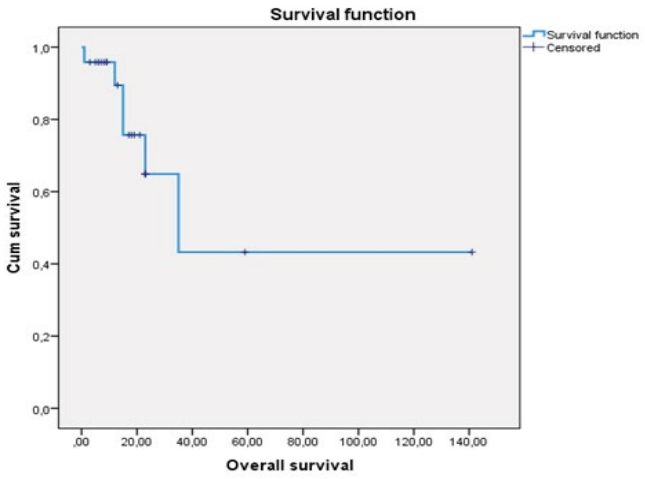

Figure 1. Overall survival in patients with chondroblastic osteosarcoma.

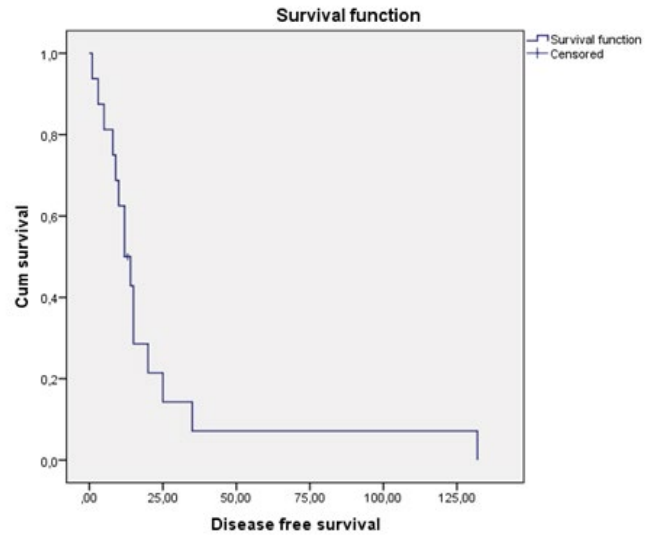

Figure 2. Disease free survival.

in patients with localized chondroblastic osteosarcoma. In patients with metastatic disease, the mean of OS and DFS were 20 months and 13 months, respectively.

The absence of clinical response after neoadjuvant chemotherapy and age >25 years were prognostic factor influencing DFS (p=0.025 and p=0.012, respectively).

Discussion

Osteosarcomas are rare. They represent less than 1% of all cancers in adults [4]. However, they are the most common primary bone neoplasms accounting for 15%-35% of primary malignant bone tumors [1]. They usually occur in adolescents and young adults between 10 and 20 years with a male preponderance [5]. Indeed, osteosarcoma is rare before 5 years, and its incidence gradually increases until the puberty. In the literature, few studies have assessed the clinical, therapeutic and prognostic factors of chondroblastic osteosarcoma. In our study, the mean age of patients was 21 years. There was an equal distribution of cases between both sexes. The most common presenting complaint were pain (n=30) and swelling (n=25). In most cases, the tumor is located in the metaphysis of the long bones [6]. It is frequently located around the knee, in lower end of femur and in the upper end of tibia. As our results show, femur and tibia were the most frequently involved sites (femur in 15 patients and tibia in 8 patients). In the upper limb, osteosarcomas most often develop in the upper end of the humerus [7]. Chondroblastic osteosarcoma represents 11% to 50% of osteosarcomas [2]. It is characterized by predominant presence of chondroid matrix according to the WHO classification [8]. Since the 1980's, multidisciplinary approach combining chemotherapy and surgery had improved the prognosis of patients with osteosarcoma. The histological response to neoadjuvant chemotherapy is based on the Huvos and Rosen classification. It assesses the percentage of tumor necrosis after neoadjuvant chemotherapy [9]. Many studies showed that the effect of neoadjuvant chemotherapy is poor in chondroblastic osteosarcoma [2,10,11]. Indeed, a study including 570 patients with osteosarcoma, showed that 75% of patients with good response to neoadjuvant chemotherapy had conventional subtype, while only 3% of them had chondroblastic osteosarcoma [3]. In fact, inf our study, a good response after neoadjuvant chemotherapy was present in only 4 cases (25%). In a study published by Tsagozis et al., good response was observed in only 18% of patients with chondroblastic osteosarcoma, while 82% of patients were poor responders. [12]. This response is a critical prognostic

factor. The absence of clinical response after neoadjuvant chemotherapy was a prognostic factor influencing disease-free-survival (p=0.025) in our study. Different medical centers may have their own preferences as to the best way to approach treatment and what chemotherapeutic regimen is best for each individual. In fact, the European Osteosarcoma Intergroup established a protocol which consists of cycles of doxorubicin and cisplatin. The brazilian protocol for non metastatic and metastatic osteosarcoma consists of cycles of doxorubicin, cisplatin and ifosfamide [13]. Surgical resection of the tumor is a mainstay for the treatment of osteosarcoma. In current study, 12 patients had salvage surgery while 10 patients had amputation. Histopathological study showed R0 margins in 86% of patients while 5% had R2 resection. Tsagozis et al. reported a local recurrence in 15% patients with chondroblastic osetosarcoma while 60% of patients had metachronous or synchronous metastases. In current study, 30% of patients with localized disease had local recurrence and 30% patients had distant metastases. OS at 2 years was 43%. DFS at 2 years was 21%. In a study published by Vyas et al., the reported OS at 2 years was 53.3% and the DFS at 2 years was 46.4% [1]. The absence of clinical response after neoadjuvant chemotherapy and age >25 years were prognostic factor influencing DFS (p=0.025 and p=0.012, respectively) in our study. The main limitations of this work were the small sample size and the retrospective nature of the study.

Conclusion

Chondroblastic osteosarcomas are aggressive cancers associated with poor prognosis and tendency for local recurrence and distant metastases. A multidisciplinary approach is mandatory. The absence of clinical response after neoadjuvant chemotherapy and age >25 years were prognostic factor influencing DFS. Novel treatment options are needed to improve outcomes in this aggressive cancer.y.

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