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Original article

Survival and prognostic factors in Chinese patients with osteosarcoma: 13-year experience in 365 patients treated at a single institution

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ABSTRACT

This study was designed to retrospectively analyze the survival and prognostic factors in Chinese osteosarcoma patients received neoadjuvant chemotherapy or/and surgery in a single institution. A total of 365 patients with pathological proved osteosarcoma undergoing neoadjuvant chemotherapy or/and surgery in a single institution between December 1999 and December 2012 were retrospectively analyzed for the demographic, tumor-related, and treatment-related variables, prognostic factors for survival rate and chemotherapy response. There were 231 males and 134 females (ratio, 1.72:1). The average age was 21 ± 10 years, with peak age between 10 and 20 years old (62%, 226/365). Of 365 patients, 319 (87.4%) suffered from primary tumor only, and 46 (12.6%) had metastases upon initial presentation. The overall 5-year survival rate was 65%. Upon univariate analysis, tumor site (femur 60.3%; other long bone 70.2%; trunk 33.6%; $P = 0.012$), primary metastases (yes 36.7%; no 68.9%; $P = 0.000$), tumor response to preoperative chemotherapy (good 89.8%; poor 47.5%; $P = 0.001$) and recurrence/metastases after treatment (yes 36.2%; no 63.8%; $P = 0.000$) were associated with higher 5-year survival rate. All factors except tumor site maintained their significance in multivariate testing. Male sex and nonconventional subtype of tumor were related to a higher likelihood of poor chemotherapy response.The absence of metastases at initial presentation, negative local recurrence or metastases after treatment, and tumor response to chemotherapy are of independent prognostic value in osteosarcoma. The overall prognostic factors and survival in Chinese patients are similar to those patients reported in western countries.

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1. Introduction

Osteosarcoma (OS) is the most common, yet still rare, histological form of primary bone malignancy, and the eighth most common childhood cancer [1]. Before the introduction of polychemotherapy, more than 90% of patients with osteosarcoma died of pulmonary metastases. A uniform treatment concept of preoperative and postoperative chemotherapy in combination with aggressive surgery has formed the basis of all consecutive neoadjuvant study protocols since 1980. Till now, some prognostic factors have been identified though they are still controversial. However, majority of early studies and recent randomized trials are conducted in Europe and North America. It has been reported that even ethnicity may have an impact on survival [2]. So, human race may be a confounding variable in survivorship analyses, which requires further analysis in clinical series. Although the number of OS patients in China is pretty large because of the gigantic population base, the clinic information of Chinese patients with OS remains very limited for the absence of clinical studies. In this retrospective study, we reviewed the records of the patients treated at our institution which was one of the authoritative bone oncology centers in China over a 13-year period, presenting the patients-related and disease-related features, analyzing treatment outcome and some possible key prognostic factors, and investigating if human race had a significant impact on the prognosis and survival.

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Table 1
Two different protocols according to the age difference.

	≦30Y: IFO + ADM + MTX		>30Y: IFO + ADM + DDP	
	Time	Dose	Time	Dose
IFO	d1–d5	2 g/m^2	d1–d5	2 g/m^2
ADM	d5	30–40 mg/m^2	d5	30–40 mg/m^2
MTX	d3	8–10 g/m^2	/	/
DDP	/	/	d6	120 mg/m^2

Notes: IFO, ifosfamide; ADM, doxorubicin; MTX, methotrexate; DDP, cisplatin.

2. Patients and methods

This study was approved by our Institutional Research Board and performed in accordance with guidelines of the Declaration of Helsinki. Medical charts between December 1999 and December 2012 were retrieved and reviewed for patients' demographics, histopathology, imaging findings, treatment modalities and clinical outcomes.

2.1. Diagnosis, staging and treatment

All patients underwent either core needle or open biopsy for establishing diagnosis, and subsequent surgical specimens were submitted for confirmation of the diagnosis. There was no histological subtype classification of osteosarcoma adopted before 2006. The subtype was classified as conventional, chondroblastic, fibroblastic, teleangiectatic, small cell and well-differential osteosarcoma, following the criteria of the World Health Organization (WHO) classification for conventional, teleangiectatic and small cell osteosarcoma [3]. For the others subtypes, criteria commonly in use were applied [4,5]. Two senior pathology experts were in charge of the work. Tumor stage was assessed according to the Enneking classification [6]. Imaging studies, including computed tomography scan (CT), magnetic resonance imaging (MRI), bone radionuclide bone scan and positron emission computed tomography (PET) were used to define the location and extension of the primary tumor, and the presence of metastasis. Since 2009, CT scan of the chest was routinely adopted to evaluate lung metastases.

Pre-operative chemotherapy commenced immediately following diagnosis from bone biopsy. The dose and chemoagents were adjusted according to the improvement of clinical symptoms including pain relief and swelling reduction, shrinkage of tumor on imaging study and patient's tolerance to the chemotherapy. Surgery was performed after three courses of pre-operative chemotherapy. Since 2007, surgical specimen was used for the evaluation of histological response to preoperative chemotherapy. The tumor response was accessed on the basis of the rate of tumor necrosis following chemotherapy [7], which was graded as "good" (90% or more tumor necrosis) or "poor" (less than 90% tumor necrosis). The, patients having good response received additional six courses of post-operative chemotherapy with the same protocol; whereas those, patients having poor response received a modified post-operative chemotherapy (exchange of methotrexate to csplatin in patients younger than 30 years) along with an increased dosage of chemo agents for six courses. The details of the dosages and schedules of the protocols are listed in Table 1 and Fig. 1. It usually took 12–15 weeks to complete the preoperative chemotherapy, and postoperative chemotherapy started in 2 weeks after surgery which was completed in 21–24 weeks.

Limb salvage and amputation were the two major surgical treatments for patients. Limb salvage was performed if there was no evidence of active systemic infection, along with a high possibility of achieving wide surgical margins on preoperative evaluation. Bone allograft was indicated when there was at least 2–3 cm or more from the projected surgical margins to the joint surface based on MRI study for limb-salvage procedure; otherwise, artificial joint replacement was required. Amputation was performed if 1) tumor involving vital neurovascular structures; 2) unresectable tumor; 3) failed preoperative chemotherapy; 4) no enough tissue left for repair after tumor resection; 5) tumor infection; or 6) patient's preference.

Patients returned for clinical follow up once every 3–6 months for the first year, then every 6–12 months. Telephone follow-up was conducted if the patients failed to appear at our clinic for routine follow-up. Chest CT and the plain radiography of the primary tumor site were obtained during follow-up for all patients. Treatment for local recurrence and/or metastases in relapsed patients was performed on an individual basis. Patients would receive similar regiment of chemo agents if they had a favorite response on previous treatment. Surgery was applied to complete remove the metastases and/or local recurrence whenever possible.

2.2. Assessment of patient, tumor, and treatment-related variables

The following variables were evaluated for the outcome: 1) Age; 2) Sex; 3) Subtype of tumors; 4) Tumor site (primary lesion); 5) Presence of metastasis; 6) Presence of pathologic fracture at diagnosis; 7) Duration of symptoms; 8) Onset of tumor-related treatment (the time from the date of initial biopsy to the first day of treatment); 9) Type of initial surgery; 10) Tumor response to preoperative chemotherapy.

2.3. Statistical analyses

All cofactors were first investigated by univariate techniques.χ^2 analysis or Student's t test was used to compare unrelated samples when appropriate. Age (an age limit of 30 years), sex, subtype of tumor (conventional vs. unconventional), tumor site (femur vs. other long bone vs. trunk), presence of primary metastases at diagnosis, duration of symptom (more or less than sixty-day), onset of tumor-related treatment (an limit of 3 weeks), surgery type (amputation vs. limb salvage) and tumor response (good vs. poor) were used in prognostic factor analyses of overall survival and tumor response.

Survival was calculated using the Kaplan-Meier method together with standard errors. Overall survival was calculated from the date of the diagnostic biopsy to death from any cause. The log-rank test was employed to compare overall survival curves. The multivariate analysis of overall survival was carried out using Cox proportional hazards regression model. Only variables with a significant prognostic value in univariate analysis were included into the multivariate models of survival. Multivariate analysis of response to chemotherapy was performed by logistic regression, with all variables assessable on the first day of tumor directed therapy being entered into the model. Significance was set at $P < 0.05$.

3. Results

From December 1999 to December 2012, a total of 445 consecutive osteosarcoma patients were identified through our medical record system. Of 445 patients, 365 patients receiving complete therapy, either pre-/post- chemotherapy or surgery, were included in this study.

3.1. Distribution of demographic and tumor-related variables

Of 365 patients, there were 231 males (63%; median age 21 ± 10.3y; range 6 to 78 years) and 134 females (37%; median age 20 ± 9.8y; range 7 to 56 years), with a median age of 21 ± 10 (range, 6 to 78 years) at diagnosis. The age distribution of the disease is

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