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ORIGINAL ARTICLE

Clinical evaluation of neoadjuvant chemotherapy for osteosarcoma

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Summary

Purpose: *To evaluate the clinical efficacy of neoadjuvant chemotherapy for treating osteosarcoma.*

Methods: *102 osteosarcoma patients in our hospital were randomly assigned into the neoadjuvant chemotherapy group and the surgery group. Patients in the chemotherapy group received neoadjuvant chemotherapy after pathological diagnosis. Surgery was performed 3 weeks after chemotherapy, followed by 4-6 cycles of postoperative chemotherapy. Osteosarcoma patients in the surgery group were operated once diagnosed and received no chemotherapy. Limb salvage or amputation surgery were performed according to the boundary of tumor resection. All patients were followed up for 24 months. The clinical efficacy, limb function, disease-free survival (DFS) and incidence of adverse events were compared between the two groups.*

Results: *Limb salvage rate and disease control survival in the chemotherapy group were higher than those of the surgery group ($p<0.05$). After follow up for 24 months, the 2-year DFS in the chemotherapy group was remarkably prolonged compared to the surgery group ($p<0.05$). No significant differences in the incidence of adverse events were observed between both groups ($p>0.05$). Limb function was markedly improved in the chemotherapy group compared with that of the surgery group.*

Conclusions: *Preoperative neoadjuvant chemotherapy for treating osteosarcoma remarkably improves the limb salvage rate, disease control rate and overall survival (OS), and constitutes an effective and safe option for osteosarcoma patients.*

Key words: *osteosarcoma, neoadjuvant chemotherapy, clinical efficacy*

Introduction

Osteosarcoma is a primary malignant bone tumor with an incidence of 0.20% among malignant tumors and 15% in primary tumors [1]. Young people 10-20 years old are highly risky for osteosarcoma. Males are more frequently affected than females, with a gender ratio of 2:1 [2]. Osteosarcoma is manifested as single lesion, occult symptoms, local pain and swelling. At the early stage of osteosarcoma, patients suffer from intermittent pain, especially at night. With the deterioration of the disease, persistent pain frequently occurs. Osteosarcoma often originates in the metaphysis of long bones, such as the distal femur and proximal humerus. In addition, metastatic osteosarcoma has very poor prognosis [3]. Osteosarcoma patients may eventually die of pulmonary metastasis due to the rather poor effectiveness of chemotherapy [4].

Amputation was the traditional therapy for osteosarcoma before the development of neoadjuvant chemotherapy, with 5-year OS as low as 19.70% [5]. Rosen et al. proposed the concept of neoadjuvant chemotherapy in the 1970s. Preoperative chemotherapy is performed to strictly control the development of distant metastasis (such as small lung lesions). Preoperative and postoperative chemotherapies are adjusted based on the results of com-

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prehensive examinations to ensure that patients receive the best optimal surgical approaches [6]. Neoadjuvant chemotherapy has shown great efficacy, and the 5-year OS has astonishingly increased to 60-70% [7]. Neoadjuvant chemotherapy exerts multiple advantages on treating osteosarcoma [8-11]. First of all, preoperative chemotherapy can eliminate micrometastases in the early-stage disease. Secondly, the primary lesion is precisely controlled or eliminated, therefore reducing the tumor adhesion to the surrounding tissues and maximizing the retention of limb function. Thirdly, chemotherapy could be timely adjusted based on the degree of tumor response. Fourthly, postoperative tumor necrosis rate can be used for evaluating the prognosis of osteosarcoma patients. The role of neoadjuvant chemotherapy in the treatment of osteosarcoma is undoubtedly beneficial to limb salvage. However, there are still 30-40% of osteosarcoma patients experiencing metastasis or recurrence due to low sensitivity to chemotherapy. Hence, it is of great significance to utilize neoadjuvant chemotherapy with proper dose and treatment duration [10].

In recent years, a large number of clinical trials have been devoted to distinguish patients who are sensitive to chemotherapy or not, so as to further improve the survival rate and reduce the recurrent risk [8]. This study analyzed key factors in neoadjuvant chemotherapy for osteosarcoma, thus providing a clinical basis for improving treatment efficacy for this disease.

Methods

Subjects

This study was approved by the ethics committee of Yuebei People's Hospital. Signed informed consents were obtained from all participants before the study entry. Enrolled were 102 osteosarcoma patients treated in Yuebei People's Hospital from January 2017 to January 2018. Inclusion criteria were: 1. Patients with pathologically diagnosed osteosarcoma; 2. No metastatic disease; 3. Patients with stage IIA or those with stage IIB that are sensitive to chemotherapy without invasion of important organs, based on the Enneking classification; 4. Osteosarcoma lesions were found at the extremities with complete clinical data. Patients with other tumors or basic diseases influencing tumor treatment were excluded.

Osteosarcoma patients were assigned into the chemotherapy group (n=52) and the surgery group (n=50).

Treatments

Tumor biopsy was performed after admission for disease confirmation. In brief, adriamycin (ADM) 80 mg/m^2/day was administered with micropump for 4 consecutive days and 120 mg/m^2 cisplatin (CDP) were intravenously administered once a day for 4 days as well. A course of neoadjuvant chemotherapy lasted for 6 days with an interval of 3-4 weeks. Routine blood tests and biochemistry examinations were regularly performed during chemotherapy. Adverse events were recorded and proper treatments were immediately given.

Efficacy evaluation

Tumor lesion size was measured by X-ray, MRI and other imaging examinations after preoperative chemotherapy. Local tumor control was assessed according to the standard criteria. Complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) were evaluated based on the follow-up data. Disease control rate was calculated as the total percent of CR and PR. Pain was assessed using VDS: a decrease ≥1 was considered as relief, and an increase ≥1 was considered as aggravation (Table 1). Adverse events were evaluated by detecting the incidence of leukocyte and platelet decline, as well as gastrointestinal reactions.

Evaluation of limb function

Postoperative limb function was evaluated based on the Enneking classification. In particular, 6 factors were evaluated, including joint mobility of the reconstructed parts, local presence or absence of self-perceived pain, stability of the artificial joints and the limbs, muscle strength levels and self-care ability [12]. A four-grade scale was used for evaluation (very good, good, fair and poor).

Table 1. Response evaluation criteria in solid tumors (RECIST)

Response criteria	*Specific standards*
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
PD	At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Statistics

SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations. Measurement data and categorical data were analyzed by the t-test and x^2 test, respectively. Kaplan-Meier method was used for survival analysis. For comparison of the subgroups according to the defined variables, the log-rank test was used. $P<0.05$ indicated the difference was statistically significant.

Results

Basic information of osteosarcoma patients

102 osteosarcoma patients were enrolled in this study, including 52 (38 males and 14 females) in the neoadjuvant chemotherapy group and 50 (35 males and 15 females) in the surgery group. In the neoadjuvant chemotherapy group, 36 patients were younger than 60 years and 16 were older than 60 years. In the surgery group, 43 patients were younger than 60 years and 7 were older than 60 years. No significant differences in sex, age, alkaline phosphatase (ALP) level and tumor size were found between the two groups ($p>0.05$, Table 2).

Table 2. Basic characteristics of osteosarcoma patients between neoadjuvant chemotherapy group and surgery group

Characteristics	*Surgery group n=50*	*Chemotherapy group n=52*
Gender		
Male	35	38
Female	15	14
Age, years		
>60	7	16
≤60	43	36
ALP (U/L)		
>200	41	42
≤200	9	10
Size of tumor cm^2		
>80	19	18
≤80	31	34

Therapeutic evaluation

35 of 52 (67.3%) patients in the neoadjuvant chemotherapy group were subjected to limb salvage surgery. In the surgery group, only 20 patients (40%) underwent limb salvage surgery ($p=0.032$, Table 3).

In the neoadjuvant chemotherapy group, the CR, PR, SD and PD were 8, 35, 5 and 4, respectively. Chemotherapy efficiency was up to 82.6%. Symptoms of pain and swelling were obviously relieved, and the local skin temperature was reduced after chemotherapy. ALP level after chemotherapy was decreased as well. Imaging studies showed that tumor size was reduced to varying degrees.

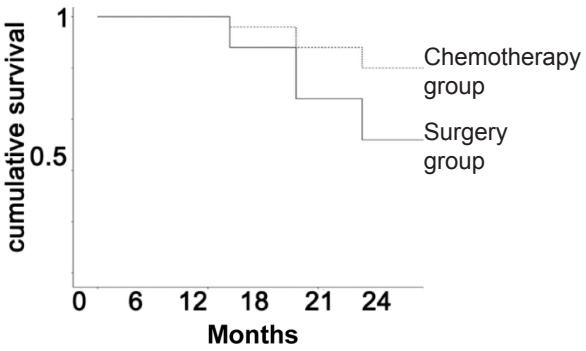

Figure 1. Postoperative survival of osteosarcoma patients between chemotherapy group and the surgery group ($p=0.046$).

Table 3. Limb salvage rate of osteosarcoma patients in the neoadjuvant chemotherapy group and surgery group

	Chemotherapy group n (%)	*Surgery group n (%)*	*Total (%)*	*p value*
Limb salvage surgery	35 (67.3)	20 (40)	55 (53.9)	0.042
Amputation surgery	17 (32.7)	30 (60)	47 (46.1)	
Total	52	50	102	

Table 4. Adverse effects of osteosarcoma patients between chemotherapy group and the surgery group

Group	*Gastrointestinal reaction (%)*	*Myelosuppression (%)*	*Liver/kidney function injury (%)*	*Other (%)*
Chemotherapy group	16.25	21.62	8.22	5.23
Surgery group	18.72	23	10.04	4.68
p	0.52	0.16	0.24	0.76

Prognosis of osteosarcoma patients

Patients were followed for at least two years. The data showed that the 2-year DFS was 74.2% and 62.3% in the chemotherapy group and the surgery group, respectively (p=0.046, Figure 1).

Limb function evaluation

Postoperative limb function was evaluated based on the Enneking classification. The overall percent of "very good" and "good" was 77.1% and 55% in patients undergoing limb salvage surgery of the chemotherapy group and surgery group, respectively (Table 4).

Adverse events

Adverse events mainly occurred during neoadjuvant chemotherapy and one week after chemotherapy, including bone marrow suppression, loss of appetite, liver function decline and hand-foot syndrome. Most patients were relieved after proper symptomatic treatments. The incidence of digestive system reactions, myelosuppression and damaged liver and kidney functions were 16.25%, 21.62% and 8.22% in the chemotherapy group, respectively. On the contrary, the incidence of these adverse events in the surgery group were 18.72%, 23.00% and 10.04%. No significant difference in the incidence of adverse events was observed between the two groups (p>0.05).

Discussion

Osteosarcoma is the most common primary malignancy of the bone, which mainly occurs in adolescents. Traditional surgical amputation poses great psychological and physical burden on affected people. With the advancement of medical technology, limb salvage surgery has gradually become the preferred therapeutic option for osteosarcoma patients. Complete resection of osteosarcoma tissue guarantees the success of limb salvage surgery [13]. It is reported that preoperative chemotherapy remarkably increases the rate of limb salvage in osteosarcoma patients [14,15]. In this study, the rate of limb salvage was 67.30% and 40.00% in the chemotherapy and surgery group, respectively, showing that preoperative neoadjuvant chemotherapy markedly elevated the rate of limb salvage.

The 5-year overall survival rate of traditional surgical treatment of osteosarcoma is less than 20% [5]. After the introduction of neoadjuvant chemotherapy in the late 1970s, the 5-year overall survival rate of osteosarcoma patients has increased to over 60% [7]. Neoadjuvant chemotherapy advocates that preoperative chemotherapy for at least 2 courses is beneficial to control the paracancer inflammation. Effective preoperative chemotherapy helps reduce disability and improve the quality of life [16]. Limb salvage surgery may increase the possibility of recurrence to some extent [17] and thorough resection of the tumor is the key factor to control the recurrence of osteosarcoma [18]. Studies have shown that neoadjuvant chemotherapy can not only reduce the local recurrence rate, but also to maximally retain the limb function [19,20].

As an important serum index of osteosarcoma, ALP level indirectly reflects the therapeutic effect of chemotherapy [15,21]. In this study, ALP level was markedly decreased after preoperative chemotherapy, suggesting the positive effect of neoadjuvant chemotherapy.

At present, doxorubicin, cisplatin, methotrexate and ifosfamide are the first-line chemotherapy drugs that are administered in different combinations in clinical treatment [22]. Neoadjuvant chemotherapy can significantly reduce the occurrence of postoperative disease recurrence and metastasis, greatly improving the clinical outcomes of osteosarcoma patients [23]. Further studies are required for developing the proper drug combinations, optimal drug dose and duration of neoadjuvant chemotherapy, thus maximizing its therapeutic efficacy.

Conclusions

Preoperative neoadjuvant chemotherapy for treating osteosarcoma remarkably improves the limb salvage rate, disease control rate and overall survival, proving its effectiveness and safety in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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