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RESEARCH

Chemotherapy Response Analysis for Osteosarcom with Intra-arterial Chemotherapy by Subcutaneous Implantable Delivery System

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Abstract To summarize the experience in intraarterial neoadjuvant chemotherapy for extremity osteosarcoma. Between January 2002 and December 2007,111 patients with stage IIB extremity osteosarcoma received preoperative intraarterial therapy with subcutaneous implantation of chemotherapy pump as well as en bloc resection, and postoperative adjuvant chemotherapy. There were 63 males and 48 females with an average age of 18 (range, 14~39 years). The time from symptom onset to hospitalization varied from several days to 6 months. The induction chemotherapy regimen includes: epirubicin [50~70 mg/m^2 by 4-hour intraarterial infusion/day for 3 day] and cisplatin [100~120 mg/m^2 by 2-hour intraarterial infusion/day for 3 days] repetitively every 2~3 weeks. Among which 24 cases only received two cycles induction chemotherapy was set to nonstandard chemotherapy group and 87 cases received three to six cycles induction chemotherapy set to standard chemotherapy group. The number of preoperative chemotherapy-cycles of standard chemotherapy group depends on the clinical and radiographic evaluation of chemotherapy efficacy. Median follow-up time was 28(8~48) months. The rate of limb preservation surgery was 89.53% (77/86) in standard chemotherapy group,and was 37.5% (9/24) in nonstandard chemotherapy group. Kaplan-Meier survival analysis showed that the 3-year overall survival rate and disease free survival rate of all the 111 cases were 68.3% and 65.9% respectively. There were significant differences in overall survival rate (38.9%, 80.0%, P=0.000), disease free survival rate (30.1%, 79.5%, P=0.000), distant metastasis rate (66.67%, 16.09%, P=0.0000) and local recurrence rate (58.33%, 13.79%, P=0.0000) between nonstandard chemotherapy group and standard chemotherapy group. Standard intraarterial neo-adjuvant chemotherapy was more effective than nonstandard intraarterial induction chemotherapy to stage IIB extremity osteosarcoma.

Keywords Osteosarcoma · Neoadjuvant chemotherapy · Arterial chemotherapy · Survival rate

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Introduction

Osteosarcoma is a kind of malignancy which often occurs in children and young adults. More than 80% of lesions locate at proximal joints. With the development of modern medical imaging and surgical technology, especially with the introduction of preoperative and postoperative chemotherapy, the outcomes of treatments for patients with osteosarcoma has improved significantly [1–4]. However in recent years, the advantages of neoadjuvant chemotherapy, which are suggested by Rosen, has been questioned and challenged by some scholars [5, 6]. Bewtween January 2002 and December 2007, 111 patients with stage IIB extremity osteosarcoma who received preoperative intraarterial therapy with subcutaneous implantation of chemotherapy

pump as well as en bloc resection, and postoperative adjuvant chemotherapy were registered in our clinical study. The cases and relevant data have been retrospectively analyzed this paper.

Patients and Methods

Patients

Inclusion criteria: (1) primary stage IIB osteosarcoma diagnosed by tissue biopsy; (2) nonmetastatic single osteosarcoma focal localized at limb long bone; (3) without other tumor history; (4) normal cardiac function; (5) with no previous treatment.

111 patients including 63 males and 48 females with an average age of 18 (range, 14~39 years) were eligible for this study. There were 11 cases occurring in proximal humerus, 7 cases in proximal femur, 4 cases in femoral shaft, 49 cases in distal femur, 32 cases in proximal tibia, 3 cases in distal tibia, 4 cases in proximal fibula and 1 case in distal fibula. The courses of diseases lasted for several days to 6 months, mostly 2–3 months. 12 patients had pathologic fracture at preliminary diagnosis or during the therapy. 87 patients (88.4%) completed 3 to 6 courses of preoperative induction chemotherapy were grouped into standard chemotherapy group. 24 patients (21.6%) refused treatment after 2 courses due to certain reasons were included into standard chemotherapy group.

Methods

Clinical Diagnoses

Osteosarcoma diagnosis contains a combination of imaging examinations including x-ray, CT scan, MRI and bone scan. After clinical and imaging evaluations, 86 patients received treatment with subcutaneous implantation of chemotherapy pump were diagnosed as osteosarcoma via biopsy performed by qualified surgical doctors. The rest 25 cases were diagnosed through puncture and biopsy at other hospitals.

Arterial Intubation Operation with Subcutaneous Implantation of Chemotherapy Pump

After local anesthesia combined with intravenous anesthesia, the proximal catheter end was introduced into the proximal end of tumor nutrient arteries. For the upper limbs, the catheter was retrogradely inserted into subclavian artery through brachial artery. For the lower limbs, the catheter was retrogradely inserted into external iliac artery through femoral artery, or retrogradely introduced it into common iliac artery on the affected side through healthy femoral artery by guidewire straddling, then inserted the catherter into external iliac artery on the affected side or femoral artery as needed. Finally the chemotherapy pump was implanted subcutaneously.

Chemotherapeutic Protocol

Arterial induction chemotherapy with subcutaneous implantation of chemotherapy pump was performed on the same day of the implantation or the next day. The induction chemotherapy regimen included: epirubicin [50~70 mg/m^2 by 4-hour intraarterial infusion/day for 3 day] and cisplatin [100~120 mg/m^2 by 2-hour intraarterial infusion/day for 3 day]. Adjuvant treatments including rehydration, diuresis, antiemetic therapy and liver-protection were performed during the chemotherapy. A treatment course consisted of 2 to 3 weeks. 3 courses constituted a treatment cycle. There was a 4-week interval every 2 treatment cycles. Leukocyte count examined via prechemotherapeutic blood cell analysis should exceed 3.8×10^9/L, platelet count should exceed 80×10^9/L, and hemoglobin level should exceed 8 g/L. During the arterial infusion with epirubicin and cisplatin, the color and temperature of the affected limb as well as pulse should be measured every hour.

The times of the preoperative chemotherapy received by patients in the standard group depends on induction chemotherapeutic evaluation. The clinical index include: ① pain in the lesion site has obviously been alleviated or disappeared; ②deep tenderness disappears; ③ local skin temperature decreases; ④ the tumor shrinks and stiffens, the tumour margin becomes sharp, and active degree between subcutaneous tissue and tumor increases; ⑤ the acitve degree of the adjacent joints increase. X-ray plain film criteria are: ① soft tissue tumor messes reduce, and the previous illegible tumor margins become sharp; ② calcification occurs in the tumor; ③ the extent of bone destruction reduces, periosteal reaction disapears, destructive cortical bone is restored to continuity. Patients in the standard group received at least 3 courses of preoperative chemotherapy. If the therapeutic effects were poor, the preoperative chemotherapy should be extended to 5–6 courses.

Histopathological criterion on postchemotherapeutic effect: Based on pathomorphological changes of tumor specimens after induction chemotherapy, curative effect can be classified into four categories: (1) good effect. (severe histological response), including stage III level 2–3, stage-IIIevel 3; (2) moderate effect (moderate histological response), including stageIIIevel 2, stageIIIevel 1 and stageIIevel 3; (3) mild effect (mild histological response), including stageIIevel 1–2 and stageIIIevel 1; (4) no effect (no histological response), namely, no pathomorphological changes in the carcinomatous tissue sample can be found.

Adjuvant chemotherapy was performed 2–3 weeks after the limb salvage operation or amputation. The dosage of chemotherapy drugs and treatment courses depended on the histopathological response of tumor specimens. Patients with severe histological response were given identical dosage of intraarterial cisplatin infusion together with intravenous epirubicin infusion every treatment course for 6 courses. Patients with moderate or mild histological response were administered every 4–5 days with intraarterial epirubicin or cisplatin chemotherapy combined with intravenous ifosfamide infusion (8~10 g/m^2) for 10–12 courses.

Amputation and Limb Salvage Procedures

According to Enneking's surgical staging system for musculoskeletal tumors, we conducted en bloc resection or radical resection of primary tumors. We performed 25 cases of amputation and 86 cases of limb salvage procedure, including 5 cases of replantation after devitalization, 64 cases of artificial joint replacement, 6 cases of extendible prosthetic replacment [7], 10 cases of radioactive seeds implantaion combined with composite prosthetic replcement, and 3 cases of operation with the use of fibular autograft.

Postoperative Examination

Patients underwent postoperative chemotherapy should have their both lungs checked by X-ray monthy, lung CT scan and full-body bone scan should be done once every half year. When the chemotherapy was finished, patients should have their both lungs checked by X-ray every 3 months, lung CT scan and full-body bone scan should be done once every half year.

Statistical Methods

The probability of survival was calculated by Kaplan-Meier method using SPSS16.0 software. The statistic significance analysis was done by log rank test. Comparisons among rates of samples were made by chi-square test. ($P<0.05$ indicated significant differences existed)

Results

Follow-up Status

By the end of December 2007, the living states of patients can be confirmed by medical records which were made according to regular clinic or telephone follow-up. Median follow-up period was 28 months. 94 cases (84.68%) were carried out with more than 1-year follow-up, 64 cases (57.66%) with more than 2-year follow-up, and 38 cases (34.23%) with more than 3-year follow-up. There were 24 cases showing lung and brain metastases as well as other distant spread, and 20 cases with limb stump and local recurrence after the operation.

Overall Survival and Event-free Survival

Figure 1 and Fig. 2 depict the overall survival and event-free survival of 111 patients with osteosarcoma. Follow-up survival rates of 3 years are shown in Table 1. It can be seen that the overall survival rate decreased year by year in 3 years. There existed significant differences among follow-up results of 1-year, 2-year and 3-year ($\chi^2=15.4479$, $P=0.0004$). The overall survival rate of 3-year follow-up decreased remarkably compared with that of 1-year follow-up ($P<0.05$). There weren't significant differences in overall survival rate between 1-year and 2-year follow-up results. No remarkable differences were found between 2-year and 3-year follow-up results either. In addition, it showed that event-free survival rate decreased year by year over 3 years. There were significant differences among follow-up results of 1-year, 2-year and 3-year ($\chi^2=14.9242$, $P=0.0006$). The event-free survival rate of 2-year follow-up decreased remarkably compared with that of 1-year follow-up ($P<0.05$). There were no significant differences in event-free survival rate between 2-year and 3-year follow-up results.

Table 2 shows the follow-up results of distant metastasis rates and local recurrence rates of 111 patients with osteosarcoma in 3 years. It can be seen that the local recurrence rates decreased year by year. There were significant differences among follow-up results of 1-year, 2-year and 3-year ($\chi^2=8.2135$, $P=0.0165$). The distant metastasis and local recurrence rates of 2-year follow-up decreased remarkably compared with that of 1-year follow-up ($\chi^2=4.4007$, $P=0.0359$), while there existed no significant differences between the results of 2-year and 3-year follow-up. Compared with the results of 1-year

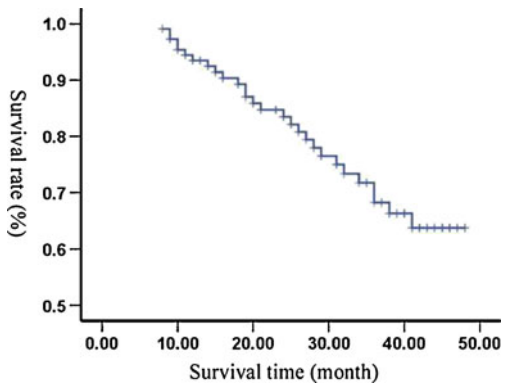

Fig. 1 Overall survival curve of 111 patients with osteosarcoma

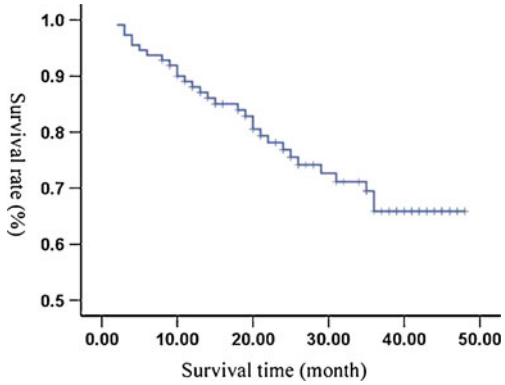

Fig. 2 Event-free survival curve of 111 patients with osteosarcoma

follow-up, the distant metastasis rates of 2-year and 3-year follow-up decreased. There were no significant differences among the three.

Survival Status of Nonstandard and Standard Intraarterial Chemotherapy Groups

Figure 3 and Fig. 4 depict the overall and event-free survival rates of patients in two groups. The 3-year follow-up overall survival rates of nonstandard and standard intraarterial chemotherapy groups were 38.9% and 80.0%, which showed significant differences (P=0.000); event-free survival rates were 30.1% and 79.5% respectively, which also presented remarkable differences (P=0.000). Table 3 shows 3-year follow-up distant metastasis rate and local recurrence rate of nonstandard chemotherapy group and standard chemotherapy group. It can be found that significant differences existed in both distant metastasis rate and local recurrence rate between the two groups (χ^2=19.4353, P=0.0000; χ^2=23.5867, P=0.0000).

Correlations between Histopathological Response of Tumor Sample and Prognosis

Table 4 shows the histopathological responses of tumor samples of 58 cases of various survival status after 2-year follow-up. Results indicated that the more severe the histopathological responses of tumor samples were, the lower the distant metastasis rates and local recurrence rates were. Differences among groups were significant (χ^2=25.6838, P=0.0000; χ^2=43.8655, P=0.0000), both the distant metastasis rates of severe histopathological responders and moderate responders were remarkably low compared with mild responders (P<0.05). In addition, there was a close correlation between the survival rate and histopathological response degree of tumor sample. It was suggested that the more severe the histopathological response of tumor samples was, the higher the survival rate was. Significant differences were found between two groups (χ^2=43.8655, P=0.0000). The survival rates of severe histopathological responders and moderate responders were remarkably high compared with mild responders (P<0.05).

Table 1 A comparison of three years follow-up survival rates of 111 patients with osteosarcoma

Survival status	Number of cases (survival rate,%)		
	Follow-up time: 1 year	2 years	3 years
Overall survival	73 (93.5)	52 (83.4)	38 (68.3)
Event-free survival	72(88.1)	50 (76.8)	36 (65.9)

Table 2 A comparison of 3 years follow-up distant metastasis rate and local recurrence rate of 111 patients with osteosarcoma

Survival status	Number of cases (survival rate,%)		
	Follow-up time: 1 year	2 years	3 years
Overall survival	13 (59.1)	9 (30.0)	4 (19.0)
Event-free survival	13 (59.1)	10 (33.3)	7 (33.3)

Postchemotherapeutic Complications

Major complication after chemotherapy was neutropenia (82%), other toxicity reactions included: gastrointestinal reaction, liver function damage, erythema, transient brachial plexus nerve damage, etc.

Main complications of this group of patients suffered from digestive tract side effect and bone marrow depress effect. The digestive tract side effects (105 cases) include nausea and vomiting. 39 cases (37.14%) suffered from the side effect of III~IV level at the first day. Marrow depress

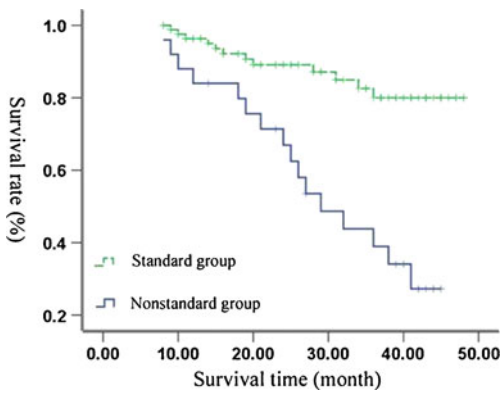

Fig. 3 Overall survival curves of standard chemotherapy group and nonstandard chemotherapy group of 111 patients with osteosarcoma

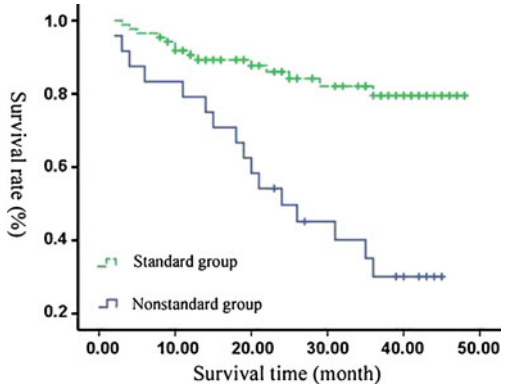

Fig. 4 Event-free survival curves of standard chemotherapy group and nonstandard chemotherapy group of 111 patients with osteosarcoma

effect happened 6~8 days after the chemotherapy. Specially, the most serious cases appeared at day 8. Neutrophilic granulocytopenia occurred in 91 cases (81.98%); III~IV level granulocytopenia occurred in 9 cases (8.10%); anemia occurred in 52 cases (46.85%), in which 5 cases (4.50%) belong to anemia over III level. Other adverse reactions include: liver function damage (9.91%), erythema (5.41%), transient brachial plexus injury (2.70%).

Discussion

Before 1970, patients with osteosarcoma were not treated with effective chemotherapy. The total survival rate of patients who received amputation were still blow 20% [8]. In 1979, the the proposed scheme of neoadjuvant chemotherapy (presurgical chemotherapy) has resulted in a significant improvement in the survival rate of patients with osteosarcoma [1]. Nowadays, the combined protocol of presurgical chemotherapy and postoperative adjuvant chemotherapy has been advocated for the treatment of most of the malignant tumor. It has been reported that intravenous neoadjuvant chemotherapy has increased the survial rate to 55%–77% [2–4]. However, the advantages of neoadjuvant chemotherapy, which are suggested by Rosen,

Table 3 A comparison of three years follow-up distant metastasis rate and local recurrence rate between nonstandard chemotherapy group and standard chemotherapy group of 111 patients with osteosarcoma

Grouping	Number of cases (occurrence rate,%)		
	Survival status:	Metastasis	Local recurrence
Nonstandard therapy group		16 (66.67)	14 (58.33)
Standard therapy group		14 (16.09)	12 (13.79)

Table 4 A comparison of histopathological responses of tumor samples of 58 cases of various survival status after 2-year follow-up

Postchemotherapeutic histopathological response	Number of cases (occurrence rate,%)			
	Survival status:	Local recurrence	Distant metastasis	Event-free survival
Mild		3 (60.0)	5 (100.0)	0 (0)
Moderate		1 (12.5)	2 (25.0)	6 (75.5)
Severe		0 (0)	0 (0)	45 (100.0)

has been questioned and challenged by some scholars [5, 6]. Goorin et al. [5] conducted a prospective multicentre trial in patients with osteosarcoma who were assigned randomly to adjuvant chemotherapy and neoadjuvant chemotherapy. Results showed that there were no significant differences in 5-year survival rates between these two groups (69%±8%; 61%±8%; P=0.8). Goorin [5] and Bacci [6] suggest that the present of tumor during preoperative chemotherapy represents a risk of metastatic spread of drug resistant osteosarcoma cell (30%).

We observed from resection procedure that effective preoperative chemotherapy can subsidise the inflammatory response in periphery of tumor and inhibit neovascularization as well as decrease tumor size. Continuous pseudomembrane is well formed in periphery of tumor, thus providing a clear boundary for en bloc resection. Certain time is necessary to have a custom-made prosthesis for the patient as well as incision healing after the operation. Therefore, we believe that the advantages are still valid: tiny metastases and satellite lesions can be eliminated immediately, and tumor regression is observed (same clinical result was found in Goorin's [5] report), thus increasing the rates of survial and limb salvage. While in Goorin's neoadjuvant chemotherapy, all patients received surgery at the 10th week [5], lacked the prediction and evaluation of tumor pathological reaction. Recentlty, Lin et al. [9] reported the outcomes of 40 cases of stage IIB osteosarcoma. For a follow-up of 2 years, the distant metastasis rates of neoadjuvant and adjuvant chemotherapy were 50.0% and 75.0%, the total survival rates were 75.0% and 37.5% (P<0.05), respectively. It is suggested that neoadjuvant chemotherapy can significantly increase 2-year survival rate of patient with stage IIB osteosarcoma, and therefore it can be considered as an ideal treatment method.

Rao et al. [10] suggested that the exposure of tumor cells to suboptimal therapy during preoperative treament could result in the development of chemoresistance, thus increasing the propensity for metastatic spread. For the 111 patients enrolled in our study, 3-year follow-up overall survival rate, event free survival rate, distant metastasis rate and local recurrence rate showed significant differences between

nonstandard intraarterial chemotherapy and standard intraarterial chemotherapy. It indicates that the standard, individualized preoperative neoadjuvant chemotherapy plays a crucial role in the increasement of survival rate as well as reduction of rates of distant metastasis and local recurrence.

Recently, high-dose multidrug chemotherapy is widely used in the adjuvant treatment of osteosarcoma [2–4, 11]. A study of the European Osteosarcoma Intergroup (EOI) [12] found that: for the group receiving intravenous treament with DOX/CDDP, the 5-year probability of event-free survival was 57% and overall survival was 64%, higher than that with DOX/CDDP treatment comprising high-dose methotrexate. Souhami et al. [13] undertook a prospective randomised multicentre trial to compare the outcomes of the following two protocols: a two-drug therapeutic regimen of 18 weeks with doxorubicin and cisplatin and a T-10 protocol multiagent regimen of 44 weeks (preoperatively vincristine, high-dose methotrexate and doxorubicin; postoperatively bleomycin, cyclophosphamide, dactinomycin, vincristine, methotrexate, doxorubicin, and cisplatin). Results showed that there were no significant differences between 3-year and 5-year survival rates. Compared with T-10 protocol, the two-drug regimen is shorter in duration, has less side effect and lower cost, and better tolerated.

We performed the neoadjuvant chemotherapy of intraarterial infusion with dose-dependent chemotherapeutic agents (cisplatin and epirubicin) for stage IIB extremity osteosarcoma using subcutaneous implantation of chemotherapy pump. The advantages of our approach lie in the following aspects: (1) The plasma concentration of veins draining the arterial infused area is 2–5 times higher by intravascular administration [14], and peripheral vasculars can achieve the same level of plasma concentration without decreasing exposure of systemic tumor [15]. (2) Compared with intravenous administration, intraarterial administration can achieve high-concentration of chemotherapeutic drugs and contribute to tumor penetration directly by physical diffusion, and promote tumor cell destruction on molecular basis, without drug inactivation and degradation in liver. (3) The side effect of local intraarterial treament is lower than that of the therapy with the same dose of intracardial injection. The former regimen can shorten the intervals of treament courses, extend treament cycle, and increase the dose intensity of chemotherapeutic drugs. (4) Standard intraarterial neoadjuvant chemotherapy can effectively control and reduce primary tumor, promote a significant increase in limb preservation rates, and reduce local recurrence rates [16]. (5) The approach with subcutaneous implantation of chemotherapy pump is a simple operative procedure which is better tolerated, thus providing a continuous administration of multiple courses or long-term treament for patients with osteosarcoma. It helps to maintain the effective time limit of high drug concentration of tumor feeding area. (6) The protocol of slow and continuous intraarterial infusion with anthracycline antibiotics (epirubicin) can help to avoid the stimulation effect of drugs on the arteries. Recently, Hugate et al. [17] reported the individualized neoadjuvant chemotherapy consisted of intravenous doxorubicin followed by intraarterial cisplatinum for osteosarcoma and malignant fibrous histiocytoma. It had been found that the 10-year survival rate was 82% and event-free survival rate was 79%. We believe that the significant increasement in the survival rate of intraarterial chemotherapy is considered as another breakthrough progress made after the invention of neoadjuvant approach. The use of dose sensitive, individualized intraarterial chemotherapy can result in better survival rate.

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