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ORIGINAL ARTICLE

S. Abe · Y. Nishimoto · K. Isu · T. Ishii · T. Goto

Preoperative cisplatin for initial treatment of limb osteosarcoma: its local effect and impact on prognosis

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Abstract *Purpose*: The significance of preoperative cisplatin (CDDP) as a single agent has not been assessed in terms of its effect on prognosis. The purpose of this multi-institution study was to assess the local effect of preoperative CDDP as a single agent as well as its impact on the prognosis of limb osteosarcoma. *Patients and methods*: The study group comprised 44 patients with stage IIB limb osteosarcoma who were treated with single-agent CDDP as initial preoperative chemotherapy. Two to five courses of CDDP (mean 2.4 courses) were administered intravenously and/or intraarterially as an initial preoperative treatment. The mean dose of CDDP was 3.0 mg/kg (2.5–3.4 mg/kg). The effect of the treatment was evaluated clinically and histologically. *Results*: The clinical and histological response rates to preoperative CDDP were 56.8% and 47.6%, respectively. The survival rate was 59.1% among all patients in the study, 64.0% among those with a grade III or IV clinical response, and 52.6% among those with a grade I or II clinical response, with no significant differences between the groups. The survival rate was 70% among patients with a grade III or IV histological response, and 54.5% among those with a grade I or II histological response, with no statistical differences between the groups. *Conclusions*: We consider that CDDP is a useful chemotherapeutic agent for preoperative induction therapy for osteosarcoma because of the excellent local effect observed. Good responders to preoperative CDDP showed a better survival rate, but a correlation between the local response to CDDP and the survival rate was not demonstrated statistically. Systemic multidrug chemotherapy should follow preoperative CDDP to diminish the microscopic foci of metastatic disease.

Keywords Osteosarcoma · Chemotherapy · Cisplatin · Preoperative chemotherapy · Chemotherapeutic response

The study presented here was a cooperative study of the Japanese Musculoskeletal Oncology Group (JMOG).

S. Abe (✉)
Department of Orthopaedic Surgery,
Teikyo University School of Medicine, Japan
E-mail: satoshi@med.teikyo-u.ac.jp
Tel.: +81-3-39644097
Fax: +81-3-53756864

Y. Nishimoto
Department of Orthopaedic Surgery,
Gifu University School of Medicine, Japan

K. Isu
Department of Orthopaedic Surgery,
National Sapporo Hospital, Japan

T. Ishii
Department of Orthopaedic Surgery,
Chiba Cancer Center, Japan

T. Goto
Department of Orthopaedic Surgery,
Tokyo University Faculty of Medicine, Tokyo, Japan

S. Abe
2-11-1, Kaga Itabashi-ku, Tokyo 173-8605, Japan

Introduction

Neoadjuvant chemotherapy is the most accepted treatment for osteosarcoma. Preoperative chemotherapy makes limb-sparing surgery possible in most cases. The importance of preoperative chemotherapy with multidrug combination regimens has been reported. Cisplatinum (CDDP), doxorubicin (DOX), high-dose methotrexate (HD-MTX), and ifosfamide are recognized as active agents and are currently used in most treatment regimens. There has been no formal assessment of these drugs to establish which is the most effective single agent and which is the most effective combination for preoperative chemotherapy. The significance of preoperative CDDP as a single agent has not been assessed in relation to its effect on prognosis in patients treated with multidrug postoperative chemotherapy. We have previously reported a multi-institutional prospective nonrandomized group investigation in which the effectiveness of preoperative CDDP chemotherapy was assessed, and found

preoperative CDDP to produce a good local effect enabling limb-sparing surgery [9]. However, its impact on prognosis was not investigated in that study.

The current study was based on our previous group study, with follow-up oncological results from the original patients together with new patients to complement the previous study. The purpose of this multi-institutional group study was to assess the effect of preoperative CDDP as a single agent and its impact on the prognosis of limb osteosarcoma.

Patients and methods

Between December 1983 and June 1993, 47 patients were entered into the study at the cooperating institutions. The diagnosis of high-grade osteosarcoma was histologically confirmed by open biopsy. The extent of disease was examined by chest tomography, chest computed tomography (CT), or technetium 99-MDP bone scan prior to preoperative chemotherapy. Three patients were excluded from the study because of the presence of lung metastasis at initial diagnosis. Thus 44 patients with stage IIB limb osteosarcoma treated with single-agent CDDP as initial preoperative chemotherapy were evaluated. The locations of lesions were as follows: femur (19), tibia (13), humerus (9), and fibula (3). The mean age of the patients was 17.1 years (7–29 years), and the mean follow-up period for living patients was 150 months (58–189 months).

On the basis of the good results achieved by Jaffe et al. [4] in osteosarcoma using intraarterial CDDP, the drug was administered through the regional artery as often as possible depending on availability of this procedure at each institution. CDDP was delivered via the intraarterial route in 21 patients (i.a. group), via both the intraarterial route and the intravenous route in 16 patients (i.a. + i.v. group), and via the intravenous route in 7 patients (i.v. group). Two to five courses of CDDP (mean 2.9 courses) were administered intravenously and/or intraarterially as initial preoperative treatment. The mean dose of CDDP was 3.0 mg/kg (2.5–3.4 mg/kg) (Table 1). All patients received postoperative multidrug combination chemotherapy with CDDP and DOX, with or without HD-MTX.

We evaluated the effect of initial preoperative CDDP treatment both clinically and histologically after its completion. For grading of clinical response we used criteria [9] modified from those of Jaffe et al. [4]. Clinical response was evaluated by combining the results of physical findings, imaging evaluation, and serum alkaline phosphatase levels. The treating physicians were asked to categorize the findings into four grades: complete response (CR), partial response (PR), no change (NC) and progression of disease (PD).

Physical findings were assessed according to the maximum circumference above the tumor, the tumor size, the degree of pain relief, and the reduction in inflammatory signs. Because MRI was not available at the time of our previous study for the majority of the patients, radiological responses were evaluated and also categorized into four grades on the basis of the radiograph, CT, technetium 99-MDP bone scan, and angiogram findings. Repair of bony destruction and regression or sclerotic changes in the extraskeletal tumor masses were assessed radiographically and by CT. Decreasing abnormal uptake on the technetium 99-MDP bone scan, and the rate of disappearance of tumor vessels on the angiogram were evaluated. The biochemical findings were evaluated in terms of the decrease in the serum alkaline phosphatase level in patients with an initial alkaline phosphatase level higher than 150% of the normal adult level.

Each finding was evaluated in terms of four grades, and the final clinical evaluation was done according to our criteria. The clinical response was evaluated by combining the results of the physical findings, the radiological findings and the biochemical findings based on the following criteria [9]:

- Grade IV effect – one or more CR
- Grade III effect – one or more PR
- Grade II effect – one or more NC
- Grade I effect – less than grade II effect

The histological response was determined by examining the surgical specimens in detail to quantify the proportion of necrotic tumor. In a grade I response, less than 50% of the tumor was necrotic. In a grade II response, 50–90% of the tumor was necrotic. In a grade III response, only microscopic foci of the tumor remained (90–99% necrosis). In a grade IV response, the tumor was totally necrotic, and no viable tumor cells were found.

The Kaplan-Meier procedure was used to evaluate survival, and the survival rates were compared using the Mantel-Cox version of the log-rank test.

Results

Clinical response

Favorable clinical responses (grades III and IV) were obtained in 25 patients, and poor responses (grades I and II) were obtained in 19 patients (Table 1). The clinical response rate to preoperative CDDP was 56.8%.

Histological response

We were able to assess the degree of necrosis in the primary tumor in 21 patients, and the average necrotic

Table 1. Clinical and histological responses

	CDDP i.a. ($n=21$)	CDDP i.a. + i.v. ($n=16$)	CDDP i.v. ($n=7$)	All patients ($n=44$)
CDDP courses	2.7 (2–4)	3.4 (2–5)	2.3 (2–3)	2.9 (2–5)
Clinical response (grade)				
I	3	1	3	7
II	4	6	2	12
III	10	9	2	21
IV	4	0	0	4
Histological response (grade)				
I (< 50% necrosis)	2	4	0	6
II (50–90% necrosis)	2	2	1	5
III (≥90% necrosis)	2	3	1	6
IV (no viable tumor cell)	2	2	0	4
Necrosis (%)	74.5 (30–100)	70 (50–90)	62.6 (20–100)	68.5 (20–100)
5-year survival (%)	71.4	43.8	57.1	59.1

ratio was 68.5% (20–100%). A good histological response (necrosis 90–99%) was obtained in 10 patients and a poor response was obtained in 11 patients. A grade IV histological response was obtained in four patients treated with intraarterial CDDP. The histological response rate to preoperative CDDP was 47.6%.

There were no differences in the clinical and histological local response rates between patients receiving or not receiving intraarterial CDDP. The correlation between the clinical response and the rate of necrosis observed was generally good, but not constant.

Surgery

The type of surgery (amputation or limb salvage) was chosen according to location and extension of the tumor. Whether to use amputation or limb-sparing surgery was decided by the individual clinical teams. Amputation was performed in 21 patients, all with a wide surgical margin except one disseminated surgical margin. The patient with disseminated surgery developed local recurrence of the disease. Limb-sparing surgery was performed in 23 patients, all with a wide surgical margin except one intralesional margin. No local recurrence was observed in the patients receiving limb-sparing surgery. There was no difference in the rate of limb-sparing surgery between patients receiving or not receiving intraarterial CDDP.

Prognosis

Of the 44 patients, 21 developed lung metastasis 2 to 17 months after surgery (mean 8.3 months). The times from surgery at which metastasis developed were 7.8 months ($n=7$, 2–17 months) in the i.a. group, 8.3 months ($n=9$, 3–13 months) in the i.a.+i.v. group, and 9 months ($n=5$, 3–12 months) in the i.a. group. Among the 21 patients, 5 (2 in the i.a. group, 3 in the i.a.+i.v group) developed bone metastasis during the course.

The status of the patients at the time of this report were as follows: 23 remained continuously free of disease, 3 showed no evidence of disease, and 18 had died of the disease. The survival rate of all patients in this study was 59.1%. According to the local clinical response, survival rates were 64.0% in patients with a grade III or IV clinical response, and 52.6% in those with a grade I or II clinical response. No significant difference was found between the groups (Mantel-Cox, $P=0.3886$; Fig. 1). The survival rate was 70% in patients with a grade III or IV histological response, and 54.5% in those with a grade I or II histological response, with no significant differences between the groups (Mantel-Cox, $P=0.4463$; Fig. 2). The survival rates were better in the group of local good responders to preoperative CDDP treatment, but the difference was not significant. There was no significant difference in survival rate between patients receiving or not receiving intraarterial CDDP (Table 1).

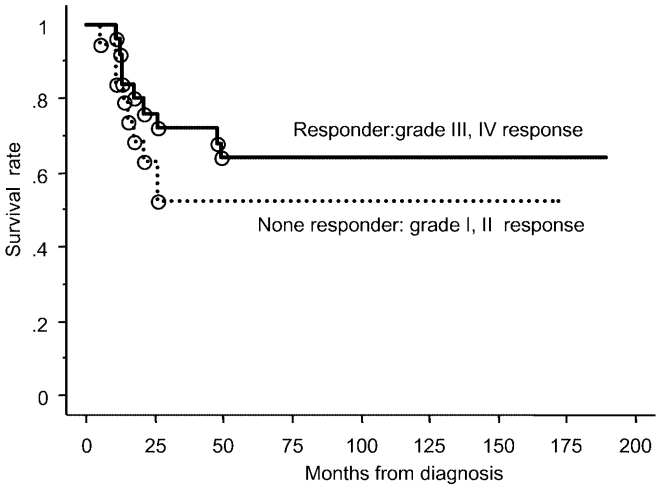

Fig. 1. Kaplan-Meier survival curves of patients with a grade I or II clinical response and those with a grade III or IV response. The difference between the groups was not significant ($P=0.3886$)

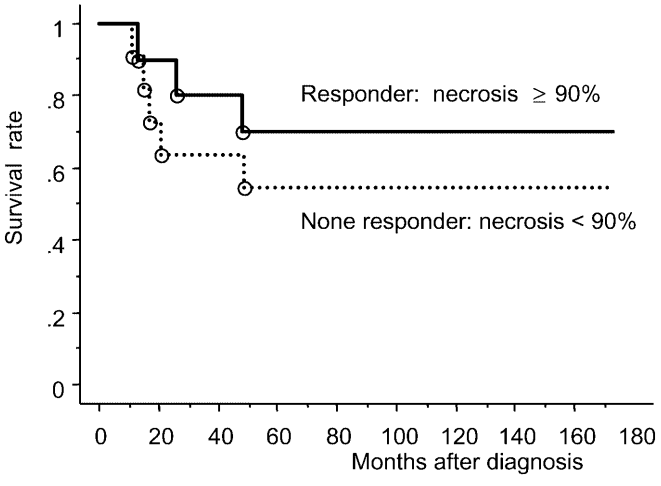

Fig. 2. Kaplan-Meier survival curves of patients with a grade I or II histological response (necrosis $<90\%$) and those with a grade III or IV response (necrosis $\geq 90\%$). The difference between the groups was not significant ($P=0.4463$)

Toxicity

In this study, both intraarterial and intravenous CDDP administration was well tolerated without severe side effects. No patients experienced severe local side effects due to intraarterial CDDP infusion.

Discussion

CDDP has been reported to be one of the most effective chemotherapeutic agents for the treatment of

osteosarcoma [2, 4, 5]. In this study, initial preoperative administration of CDDP led to extensive destruction of the tumor. The clinical response rate to preoperative CDDP was 56.8%, and the histological response rate was 47.6%. We also compared preoperative CDDP with other preoperative chemotherapeutic regimens that did not include CDDP. A good histological response was seen in 28% of patients treated with preoperative HD-MTX, vincristine, and a combination of bleomycin, cyclophosphamide, and dactinomycin (BCD) in a Children's Cancer Group study [8]. Single-agent HD-MTX preoperative chemotherapy led to a good histological response in 12% of patients [1].

Our finding of a better local effect with single-agent CDDP indicates that CDDP should be used as preoperative chemotherapy to enhance the likelihood that safer limb-sparing surgery will be successful. We believe that CDDP is the best chemotherapeutic agent as preoperative induction therapy for osteosarcoma. Because CDDP produces an excellent local response, better local control can be achieved and the subsequent limb salvage surgery can be accomplished safely.

In previous studies, it has been accepted that the histological response to preoperative chemotherapy strongly predicts subsequent survival [3, 6]. In this study, the correlation between local response and survival rate was analyzed. A better survival rate was obtained in the group of good responders, but we could not demonstrate a significant difference in prognosis in relation to the local response to CDDP treatment. A possible explanation for the discrepancy between local response and general outcome is that local intensive chemotherapy including intraarterial CDDP administration may have raised the rate of local response, but may not have destroyed the exhibiting micrometastases. Intraarterial CDDP administration was employed in approximately 80% of the patients in this study. Moreover, the local concentration of CDDP was higher in patients treated with intraarterial CDDP than in patients receiving intravenous CDDP.

Jaffe et al. have recommended local intensive treatment with intraarterial CDDP infusion, and have reported good histological results in the treatment of osteosarcoma [4, 5]. The antitumor effect of CDDP is dose dependent, and intraarterial administration increases the local platinum concentration compared to the systemic serum platinum concentration. This local dose intensification may have resulted in an alteration in the response to chemotherapy between the local tumor and exhibiting micrometastases. We consider that systemic multidrug chemotherapy should follow preoperative CDDP to diminish microscopic foci of metastatic disease.

In the study of the multidrug intensified preoperative regimen, the authors also reported this discrepancy between local response and general outcome of the systemic treatment. In this Memorial-Sloan Kettering Cancer Center study, the two different preoperative regimens of HD-MTX and BCD with and without CDDP/DOX were compared. A better histological response in the intensified regimen including preoperative CDDP/DOX was found, but there was no difference in the overall survival rate. The authors concluded that the intensified preoperative chemotherapy produced a better histological response but did not improve the survival rate. Tumor necrosis is not always a reflection of chemotherapy effectiveness. More studies of the biology of osteosarcoma are needed to clarify the discrepancy [7].

The number of patients enrolled in this study was relatively small, and the power of the study was limited. Nevertheless, the possibility exists that local response to preoperative CDDP did not correlate with systemic disease control, and systemic multidrug chemotherapy should follow preoperative CDDP to diminish the microscopic foci of metastatic disease. Further studies with a large number of patients are needed to clarify this discrepancy between local response and general outcome. New modalities to evaluate the effectiveness and clinical outcome of the treatment in osteosarcoma are mandatory.

We conclude first that CDDP is a useful chemotherapeutic agent as preoperative induction therapy for osteosarcoma because of the excellent local effect observed, and second that good responders to preoperative CDDP show a better survival rate, but the correlation between local response to CDDP and survival rate was not demonstrated in the statistical analyses. Systemic multidrug chemotherapy should follow preoperative CDDP to diminish microscopic foci of metastatic disease.

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