Neoadjuvant Chemotherapy: Osaka University Osteosarcoma (OOS) Regimen

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Abstract

Objective: The purpose of this study is to evaluate the efficacy of a four-drug regimen neoadjuvant chemotherapy for osteosarcoma with doxorubicin, cisplatin, methotrexate, and ifosfamide for patients ≤40 years of age with nonmetastatic osteosarcoma of the extremity.

Methods: From 1997 to 2012, 82 patients were evaluated. Treatment consisted of ten courses of chemotherapy and wide local excision. Preoperatively, patients received two courses of doxorubicin (90 mg/m^2)/cisplatin (120 mg/m^2) combination and high-dose ifosfamide (15 g/m^2). Postoperatively, patients received two courses of doxorubicin/cisplatin combination, high-dose ifosfamide, and high-dose methotrexate (12 g/m^2 on consecutive weeks).

Results: There were 2 patients with local recurrence, 17 patients with lung metastasis, and 1 patient with bone metastasis. At the last follow-up, 61 patients were continuously disease-free, 11 patients had no evidence of disease, 3 patients

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were alive with disease, 6 patients died of disease, and 1 patient died of treatment-related toxicity. The 5-year and 10-year event-free survival rates were 77 % and 73 %, respectively. The 5-year and 10-year overall survival rates were 95 % and 90 %, respectively.

Conclusion: A four-drug regimen neoadjuvant chemotherapy for osteosarcoma with doxorubicin, cisplatin, methotrexate, and ifosfamide was feasible. The survival rates were similar or better than previous studies. This study shows that this four-drug ten-course regimen can be an effective treatment for osteosarcoma.

Keywords

Osteosarcoma • Chemotherapy • High-dose ifosfamide • Histological response • Cumulative dose

8.1 Introduction

The prognosis for patients with osteosarcoma has greatly improved with the introduction of multidrug chemotherapy [1–3]. It is generally accepted that there are four active drugs against osteosarcoma: doxorubicin (DOX), cisplatin (CDDP), methotrexate (MTX), and ifosfamide (IFM) [4, 5]. However, there is a controversy as to which combination is the most effective. IFM has been used mainly in regimen for poor responders or relapse [6, 7]. Also, IFM has been used as a single agent or with a combination of other agents such as DOX, CDDP, or etoposide [8–11]. When used as a single agent, the dose of IFM varied from 10 to 15 g/m^2 [12–14].

At Osaka University Orthopaedic Oncology Group, neoadjuvant chemotherapy with high-dose MTX (HD-MTX) and DOX followed by adjuvant chemotherapy with the same drugs was first introduced in 1976 for the treatment of osteosarcoma (OOS-A regimen). In 1982, CDDP was added and DOX was administered intra-arterially (OOS-B regimen) to achieve a higher intratumor concentration. Standard-dose IFM (10 g/m^2) was added to the OOS-B regimen (OOS-C regimen) in 1989 [12]. From 1997, the OOS-D regimen consisting of DOX/CDDP, HD-MTX, and high-dose IFM (HD-IFM) (15 g/m^2) was introduced. The purpose of this study is to evaluate the efficacy of the OOS-D regimen neoadjuvant chemotherapy for patients $\leq$40 years of age with nonmetastatic osteosarcoma of the extremity.

8.2 Patients and Methods

Patients were enrolled in our group of five institutions (Osaka University Graduate School of Medicine and four affiliated cancer centers). Eligibility criteria were biopsy-proven diagnosis of primary conventional high-grade osteosarcoma of the extremity with no known metastasis at presentation; under 40 years of age; normal hepatic, renal, cardiac function; and no prior therapy. Primary tumor was evaluated

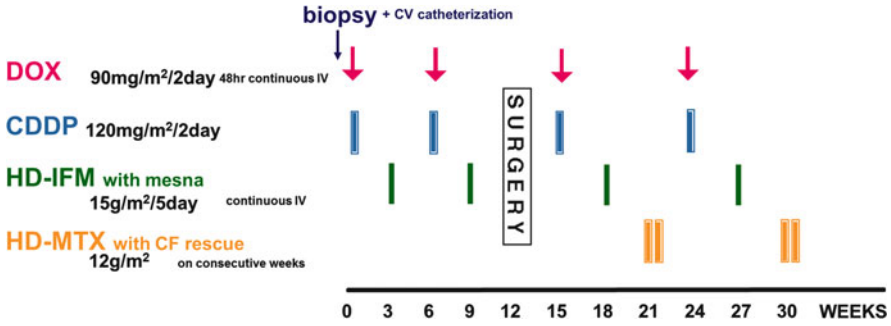

Fig 8.1 OOS-D regimen

by plain radiograms, magnetic resonance imaging (MRI) scans, and/or computed tomography (CT) scans. Screening for metastasis was evaluated by chest plain CT scan and bone scintigraphy.

OOS-D regimen: Chemotherapy consisted of DOX/CDDP (courses 1, 3, 5, 8), HD-IFM (courses 2, 4, 6, 9), and HD-MTX (courses 7, 10) according to the schedule and dose shown in Fig. 8.1. Each course was administered every 3 weeks. DOX was administered as a 48-h continuous infusion with a dose of 90 mg/m^2, and CDDP was administered intravenously for 4 h for 2 days at a daily dose of 60 mg/m^2. IFM was administered as a 5-day continuous intravenous infusion with a total dose of 15 g/m^2 with mesna uroprotection. MTX was administered as a 6-h infusion with citrovorum factor rescue every 6 h beginning 24 h after the start of MTX infusion. Sodium bicarbonate was administered for adequate alkalinization to keep urinary pH more than 7.0. One course of HD-MTX included two weekly administration of MTX. All the treatment was done as inpatient.

Complete blood count (CBC) and renal and hepatic functions were monitored before and after each chemotherapy administration. Granulocyte colony-stimulating factor was given to patients with grade 3 or 4 leukopenia. Chemotherapy was delayed or dose reduction (80 %) was allowed if granulocyte count was less than 1,000/mL, or platelet count was less than 100,000/mL, or there was renal or hepatic disorder. Normal renal function was required before each chemotherapy administration.

Surgical resection of tumor was scheduled after four courses of chemotherapy. All patients received limb salvage surgery. In principle, en bloc wide margin resection of the tumor was performed. Reconstruction was performed with either prosthetic replacement or intraoperative radiated autologous bone graft (IORBG) [15]. Postoperative chemotherapy was to start 3 weeks after surgery.

Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Histological response to chemotherapy was evaluated in resected tumor specimens. Good response was defined as total or more than 90 % necrosis of the tumor. Poor response was defined as lesser than 90 % necrosis of tumor [16].

8.2.1 Statistics

The event-free survival (EFS) was calculated from the date of start of chemotherapy until the date of first event including recurrence (local or distant) or chemotherapy-related death or the date of last follow-up examination. The overall survival (OS) was calculated from the date of start of chemotherapy until the date of death or the date of last follow-up examination. Survival curves were estimated using the Kaplan-Meier method and were compared by means of the log-rank test. Statistical analyses were performed using JMP ver. 10.0 software (SAS institute, North Carolina).

8.3 Results

From 1997 to 2012, out of 271 patients treated for osteosarcoma at our institute, 82 patients were eligible for this study. The patient characteristics are listed in Table 8.1. The median follow-up period for surviving patients was 113 months (range 29–193 months).

Table 8.1 Patient characteristics

	No.	%
Age (years)		
Median	16	
Mean	17.2	
Range	7–37	
Gender		
Male	54	66
Female	28	34
Surgical stage		
IIA	7	9
IIB	75	91
Site		
Femur	43	52
Tibia	22	27
Humerus	11	13
Fibula	6	7
Histological subtype		
Osteoblastic	51	62
Chondroblastic	9	11
Fibroblastic	6	7
Telangiectatic	5	6
Small round cell	1	1
Not specified	10	12

8.3.1 Chemotherapy Compliance and Toxicity

Of the 82 patients, 59 (72 %) completed all ten courses of chemotherapy. Of the courses uncompleted, HD-MTX was skipped the most at eight times. This was due to delayed excretion of MTX in the first week of HD-MTX, and the second week was skipped. HD-IFM was skipped four times due to severe prolonged hematological toxicity from the previous course. Other causes for discontinuation were renal disorder, wound infection, and patient's request.

One patient died as a result of chemotherapy-related toxicity. A 15-year-old boy died from acute heart failure 2 months after completion of therapy. There were no other patients who reported with cardiomyopathy. All patient experienced grade 4 hematologic toxicity.

8.3.2 Histological Response

During the preoperative chemotherapy, no clinical or radiological progression of disease was confirmed. Histological response to chemotherapy was good in 39 patients (56 %) and poor in 31 patients. The histological response of 12 patients could not be obtained because histological examination of the whole tumor was not available.

8.3.3 Patient Outcome

At the last follow-up, 61 (74 %) patients were continuously disease-free, 11 (13 %) patients were alive with no evidence of disease, 3 (4 %) patients were alive with disease, 6 (7 %) patients died of disease, and 1 (2 %) patient died of treatment-related toxicity. The 5-year and 10-year EFS rates were 77 % (95 % CI, 67–84 %) and 73 % (95 % CI, 62–82 %), respectively (Fig. 8.2). The 5-year and 10-year OS

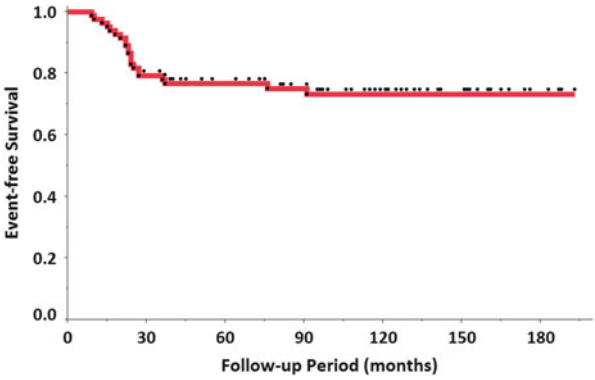

Fig 8.2 Event-free survival of all patients

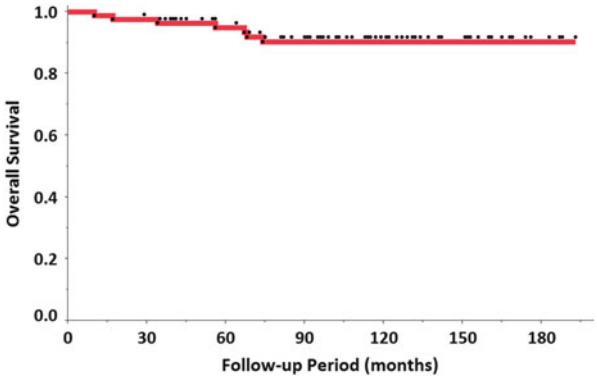

Fig 8.3 Overall survival of all patients

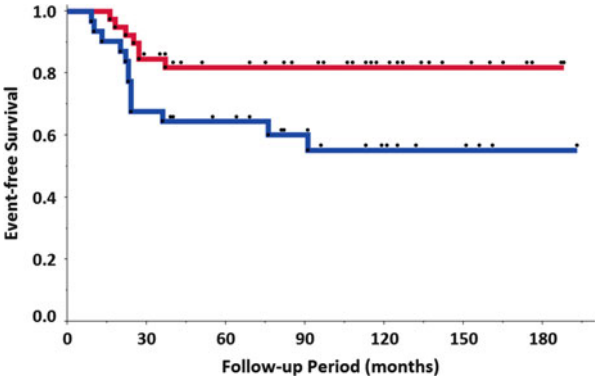

Fig 8.4 Event-free survival: good responder (*red*); poor responder (*blue*): $p = 0.025$

rates were 95 % (95 % CI, 87–97 %) and 90 % (95 % CI, 81–95 %), respectively (Fig. 8.3).

Two patients (2 %) had local recurrence 23 and 24 months after the start of treatment. Both patients had amputation of the affected limb. Seventeen patients (21 %) had lung metastasis and one patient (1 %) had bone metastasis. Median time to metastasis was 23.5 months (range 9–91 months). All patients underwent metastasectomy. The 3-year and 5-year post-relapse survival rates were 84 % and 67 %, respectively.

For good responders, the 5-year and 10-year EFS rates were both 82 % and were significantly better than poor responders at 65 % and 55 % ($p = 0.025$), respectively (Fig. 8.4). The 5-year and 10-year OS rates for good responders were 100 % and 94 % and were better than those for poor responders at 87 and 82 % though not statistically significant ($p = 0.11$) (Fig. 8.5).

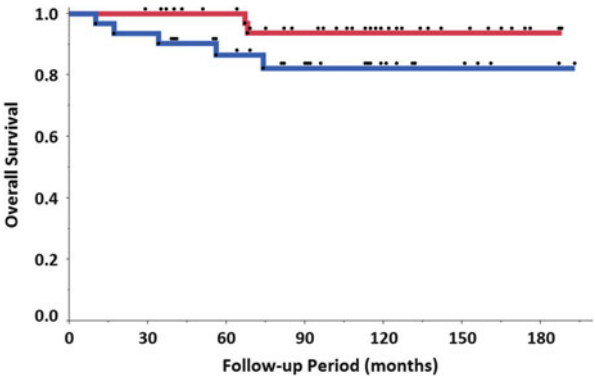

Fig 8.5 Overall survival: good responder (*red*); poor responder (*blue*): $p = 0.11$

8.4 Discussion

The prognosis for patients with osteosarcoma has greatly improved with the introduction of multidrug chemotherapy. At our institution, since the introduction of chemotherapy, the 5-year OS has improved from 13 % to 49 % (OOS-A) to 72 % (OOS-B) to 78 % (OOS-C) [12]. The current OOS-D regimen has improved the 5-year OS to 95 % (Table 8.2). In planning for the OOS-D regimen, there were discussions on whether MTX should be included in preoperative chemotherapy. Previously at our institute, we had two cases of severe MTX excretion delay which led to the delay of chemotherapy and progression of disease. Because of this experience, we decided to omit HD-MTX from the preoperative regimen and include it only in the postoperative regimen. The histological response rate of this study was 56 % which was about equal to other studies even without MTX [14, 17].

IFM is widely used in the treatment of osteosarcoma. But IFM has been used mainly in patients for poor responders or relapse. Also, IFM has been used as a single agent or with a combination of other agents such as DOX, CDDP, or etoposide. When used as a single agent, the dose of IFM varied from 10 to 15 g/m^2. There are only a few studies with HD-IFM given first line in a preoperative phase [13, 14, 18]. Bacci et al. first reported in a pilot study that HD-IFM had a better EFS and OS than previous protocols, but in the ISG/SSG 1 study, Ferrari et al. reported that there was no benefit in oncological results [13, 14]. In this study, we report a 5-year EFS of 77 % and a 5-year OS of 95 %. There was a significant difference between the EFS rates for histological response. The oncological results were better than reports by other groups, even though the response rate was about the same with other reports (Table 8.3). Even the EFS and OS rates of poor responder were in the same range as other reports. This could be because of the contribution of HD-MTX and HD-IFM given postoperatively.

The addition of HD-IFM has been reported to have an increase in toxicity. The acute toxicity, mainly hematological and renal toxicity with Fanconi-like syndrome, has been reported [14]. In our study all patients experienced grade

Table 8.2 Overall survival of OOS regimens [12]

	5-year OS
No chemotherapy (~1976)	13 %
OOS-A (~1982)	49 %
OOS-B (~1989)	72 %
OOS-C (~1996)	78 %
OOS-D (1997~)	95 %

Table 8.3 Survival rates of regimen that include ifosfamide

Study group	Patients	Period	Regimen	5Y-EFS (%)	5Y-OS (%)
EOI [11]	43	1986–1990	DOX+CDDP+IFM 6 g/m^2	56	62
COG [17]	662	1993–1997	HD-MTX+DOX+CDDP (MAP)	64[a]	71[a]
			MAP+MTP-PE	63[a]	75[a]
			MAP+IFM 9 g/m^2	58[a]	70[a]
			MAP+IFM+MTP-PE	71[a]	81[a]
ISG/SSG 1 [14]	182	1997–2000	MAP+HD-IFM 15 g/m^2	64	77
OOS-D	82	1997–2012	MAP+HD-IFM 15 g/m^2	77	95

EOI European Osteosarcoma Intergroup, *COG* Children's Oncology Group, *ISG/SSG* Italian Sarcoma Group/Scandinavian Sarcoma Group
[a]6Y EFS/OS

4 hematologic toxicity, but we did not have any patient with severe renal toxicity. This could be because all the treatment was done inpatient, and there could be careful monitoring of hydration and urine output. Another toxicity associated with HD-IFM is infertility in males [19]. We have not analyzed the sperms of the patients, but two patients (both age 16 at diagnosis) have fathered children. The only fatal toxicity experienced was one patient with acute heart failure. Cumulative dose of DOX has been considered a risk for cardiomyopathy, but in this regimen, the total dose of DOX (360 mg/m^2) was considered low risk [20]. Another risk for severe toxicity is the cumulative dose of all the drugs. In this regimen, the cumulative dose of DOX was 360 mg/m^2, CDDP was 480 mg/m^2, MTX was 48 g/m^2, and IFM was 60 g/m^2. It compared to have a better balance of the four drugs than other regimens (Table 8.4).

In conclusion, the OOS-D regimen had an excellent outcome for patients with osteosarcoma of the extremities. This regimen consists of a well-balanced use of the four key drugs and was feasible and well tolerated. This study was not randomized and the sample size was not large. A larger study and longer follow-up will be important to assess benefits and long-term toxicity of this regimen.

Table 8.4 Cumulative dose

Study group	Subgroup	DOX (mg/m^2)	CDDP (mg/m^2)	MTX (g/m^2)	IFM (g/m^2)
EOI, 1999 [11]		450	300		18
COG, 2008 [16]	MAP	450	480	144	
	MAP+IFM	450	480	144	45
ISG/SSG 1, 2005 [14]	Good responder	330	480	48	60
	Poor responder	330	690	60	75
OOS-D		360	480	48	60

EOI European Osteosarcoma Intergroup, *COG* Children's Oncology Group, *ISG/SSG* Italian Sarcoma Group/Scandinavian Sarcoma Group

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