RESEARCH ARTICLE

Continuous-infusion Ifosfamide and Doxorubicin Combination as Second-Line Chemotherapy for Recurrent or Refractory Osteosarcoma Patients in China: a Retrospective Study

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Abstract

Objective: The aim of this retrospective study was to evaluate the feasibility and efficacy of response to continuous-infusion ifosfamide and doxorubicin combination as second-line chemotherapy for patients with recurrent or refractory osteosarcoma. Materials and Methods: Eighteen recurrent or refractory osteosarcoma patients who were treated with continuous-infusion ifosfamide and doxorubicin combination between May 1999 and April 2011 were included in the analysis. Ifosfamide at 12g/m^2 was administered by intravenous continuous infusion over 3 days, and doxorubicin 60mg/m^2 was administered as an intravenous bolus injection on day 1. The combination therapy was repeated every 3 weeks. Treatment was continued until evidence of disease progression or unacceptable toxicity. Results: The patients (ages 7-53 years) received a total of 42 cycles of chemotherapy (median: 2 courses; range: 2-5 courses). The overall response rate was 0% and the disease control rate was 22.3%, with four patients having stable disease. The median time to progression and overall survival time were 2 months (range: 2-5 months) and 9 months (range: 3-29 months), respectively. Major severe toxicities were leucopenia 7 (38.9%), nausea and vomiting 3 (16.7%) and alopecia 9 (50%). There were no treatment-related deaths. Conclusions: In our experience, continuous-infusion ifosfamide and doxorubicin combination therapy at this dosage and schedule was found to be well tolerated and moderate effective, which could be considered as salvage therapy for patients with recurrent or refractory osteosarcoma. Further assessment is necessary to confirm the safety and efficacy of this treatment.

Keywords: Continuous-infusion - ifosfamide - doxorubicin - salvage chemotherapy - osteosarcoma

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Introduction

Osteosarcoma is the most common malignant primary bone tumor predominantly affecting young people, comprising about 20% of primary bone sarcoma (Ta et al., 2009). The introduction of multi-disciplinary treatment (surgical resection in conjunction with perioperative multi-agent chemotherapy) improved the survival of osteosarcoma patients dramatically (Sluga et al., 1999; Bacci et al., 2002; Hawkins et al., 2003; Wilkins et al., 2003; Kudawara et al., 2013). However, the prognosis of patients who present with unresectable or relapsed disease remains poor (Bielack et al., 2002; Ferrari et al., 2003). Studies showed that second line chemotherapy might improve the outcome of these patients (Saeter et al., 1995; Ferrari et al., 2003). However, the optimal treatment strategy for these patients is still not defined.

The key drugs in the standard chemotherapy for osteosarcoma include high-dose methotrexate, cisplatin and doxorubicin (Meyers et al., 2005). Ifosfamide is also reported to be an active agent for osteosarcoma by the schedule of a bolus dose in 30-60 min over 2-5 days (Harris et al., 1995; Kobys et al., 2013). Recently, several retrospective clinical trials had been conducted to assess the efficacy and toxicity of continuous-infusion ifosfamide-based combination therapy for sarcomas, but the results were controversial. And what's more, pathologic histologies of the included patients, the dosages of ifosfamide and chemotherapy schedules in the studies were diverse (Palumbo et al., 1997; Singer et al., 1998; Cartei et al., 2003; De Pas et al., 2011).

Therefore, the role of continuous-infusion ifosfamide-based combination therapy in refractory or recurrent high-grade osteosarcoma is still not well defined. As a result, we undertake this retrospective study to assess the efficacy and toxicity of continuous-infusion ifosfamide and doxorubicin combination therapy for recurrent or refractory high-grade osteosarcoma. As far as we know, this is the largest retrospective study so far to investigate continuous-infusion ifosfamide and doxorubicin combination therapy for recurrent or refractory osteosarcoma patients.

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Materials and Methods

Patients and treatment

Eighteen patients with relapsed and refractory osteosarcoma who received continuous-infusion ifosfamide and doxorubicin combination therapy as second-line chemotherapy at our institution between May 1999 and April 2011 were selected for this retrospective case series study, according to the following criteria:*i*) histological confirmation of diagnosis; *ii*) prior treatment (completed >3 weeks before trial entry) consisted of standard high-grade osteosarcoma chemotherapy agents including doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate; *iii*) disease progression with radiological evidence; *iv*) Karnofsky performance status ≥70 with a life expectancy >3 months; *v*) adequate renal, hepatic, and hemopoietic function. The patients' clinical characteristics such as age, gender, pathologic subtypes, and performance status were collected for statistical analysis.

Ethical approval for the study was provided by the independent ethics committee, Sixth people's Hospital, Shanghai JiaoTong University. Informed and written consent was obtained from all patients or their advisers according to ethics committee guidelines.

The ifosfamide-doxorubicin regimen was administered as follows: *i*) ifosfamide 12 g/m^2 i.v. as continuous infusion over 3 days; *ii*) mesna 16 g/m^2 i.v. as continuous infusion over 4 days; *iii*) doxorubicin 60mg g/m^2 i.v. bolus on day 1. Every 3-week treatment schedule was designated as one cycle, and a cycle of chemotherapy was given every 3 weeks. Prophylactic 5-hydroxytryptamine (5-HT3) receptor antagonists and other antiemetic treatments were given to all patients. Granulocyte colony-stimulating factor was used when patients with febrile neutropenia or Grade 4 neutropenia were judged as requiring its administration by physician-in-charge.

Table 1. Patient Characteristics

Features	n	percent
Gender		
Male	14	77.8
Female	4	22.2
Age at study entry (years)		
Median (range)	16.5 (7-53)	
<18	10	55.6
≥18	8	44.4
KPS		
90	6	33.3
80	9	50
70	3	16.7
Location of primary tumor		
Upper limbs	5	27.8
Lower limbs	11	61.1
Non-extremities	2	11.1
Histotype		
Conventional	15	83.3
Other	3	16.7
Metastatic at diagnosis		
Yes	5	27.8
No	13	72.2
Adjuvant chemotherapy		
Yes	12	66.7
No	6	33.3
Patterns of relapse		
Lung metastasis	11	61.1
Lung metastasis + local recurrence	3	16.7
Lung metastasis + bone metastasis	1	22.2

Patient assessment

Tumor response was usually evaluated every two chemotherapy cycles by computed tomography (CT)/ magnetic resonance imaging (MRI) scan according to the Response Evaluation Criteria in Solid Tumors (RECST) (Therasse et al., 2000). Treatment responses were classified as: *i*) complete response (CR), *ii*) partial response (PR), *iii*) progression disease (PD), and *iv*) stable disease (SD). Only patients with SD, PR, and CR continued chemotherapy.

The maximum toxicity was recorded for each cycle of chemotherapy according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 3.0). All toxicities were classified into four levels; the following toxicities were recorded: white blood cell count, platelet count, hemoglobin, gastrointestinal toxicities (nausea and vomiting), fatigue, alopecia, impaired liver function, impaired renal function, cardiotoxicity, and hematuresis.

Statistical analysis

A retrospective analysis in terms of response rate, progression-free survival (PFS) and overall survival (OS) was performed. The Kaplan-Meier method was used to estimate the PFS and the OS. OS was defined as the time from the start of treatment to death from any cause. Patients alive at the time of analysis were censored at the date of last follow-up. PFS was measured from the start of treatment to progression of the disease or death from any cause. Patients who were alive and progression free at the last follow-up were censored. Duration of response was defined as time from the date of the first objective response until the time of patient progression or death. Data were presented as percentage or median plus range unless otherwise specified. All analyses were performed with SPSS soft-ware version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient Characteristics

Between May 1999 and April 2011, 18 patients with relapsed and refractory osteosarcoma were treated with continuous-infusion ifosfamide and doxorubicin combination therapy in our institution. Table 1 lists the features of the analyzed patients. The patients' median age was 16.5 years (range 7-53 years), and 77.8 % (14/18) were male. Most patients (83.3.0 %) had a KPS of ≥80, and 27.8 % had metastatic disease at diagnosis. After primary therapy, eleven patients had lung metastasis alone, three patients had local recurrence with lung metastasis and four patients had bone metastasis with lung metastasis. 66.7 % received adjuvant chemotherapy.

Efficacy and safety

All patients received at least two cycles of continuous-

Table 2. Details of Response to Continuous-icccccnfusion Ifosfamide and Doxorubicin Chemotherapy

Patient number	Age (year)	Sex	Site of primary	Metastases at diagnosis	Site of relapse	Number of cycles	Best response to continuous-infusion ifosfamide and doxorubicin combination therapy
1	7	Male	Tibia	No	LM+BM	2	PD
2	12	Male	Tibia	No	LM+BM	2	PD
3	25	Male	Humerus	No	LM	3	SD
4	16	Male	Tibia	No	LM	2	PD
5	17	Male	Femur	No	LM	5	SD
6	43	Male	Femur	Lung	LM+LR	3	SD
7	16	Male	Tibia	Lung	LM	2	PD
8	36	Male	Ribs	No	LM	2	PD
9	41	Male	Maxilla	Lung	LM+LR	2	PD
10	12	Female	Femur	Lung	LM	3	SD
11	16	Female	Humerus	No	LM	2	PD
12	53	Male	Humerus	No	LM	2	PD
13	15	Female	Tibia	No	LM	2	PD
14	15	Male	Femur	Lung	LM	2	PD
15	20	Male	Humerus	No	LM+LR	2	PD
16	15	Female	Femur	No	LM+BM	2	PD
17	28	Male	Humerus	No	LM	2	PD
18	20	Male	Femur	No	LM+BM	2	PD

*LM, lung metastasis; BM, bone metastasis; LR, local recurrence; PD, progression disease; PR, partial response; SD, stable disease

Table 3. Tumor Response to Continuous-Infusion Ifosfamide and Ddoxorubicin Combination at two Cycles

Response	n	Percen
Total assessable patient	18	100
CR	0	0
PR	0	0
SD	4	22.3
PD	14	77.7
Overall response rate (CR + PR)	0	
Tumor control (CR + PR + SD)	4	22.3

*CR, complete response; PR, partial response; PD, progression disease; SD, stable disease

infusion ifosfamide and doxorubicin combination therapy (median, 2 cycles per patient; range: 2-5 cycles) and a total of 42 cycles was administered. All of 18 patients were available for tumor response evaluation. After two cycles of treatment, 12 patients changed chemotherapy regimen due to disease progression, 2 patients refused to receive more chemotherapy due to personal or economic reasons, and 1 patient received five cycles of continuous-infusion ifosfamide and doxorubicin combination therapy. We observed no CRs, no PRs, and four SDs (Table 2). The overall response rate and disease control rate were 0 and 22.3%, respectively (Table 3). At the cut-off date, the median OS was 9 months (range: 3-29 months), and the median PFS was 2 months (range: 2-5 months).

We recorded no drug-related deaths. In general, chemotherapy-related adverse events were limited to Grade 1 or 2. We noted the following Grade 3 and 4 toxic effects: leucopenia 7 (38.9%), nausea and vomiting 3 (16.7%) and alopecia 9 (50%). Table 4 summarizes the main side effects and all Grade 3 and 4 adverse events.

Discussion

There is currently no standard salvage treatment as second-line chemotherapy for recurrent or refractory osteosarcoma. Several new agents such as topotecan (Seibel et al., 2007), irinotecan (Crews et al., 2004; Bagatell et al., 2014), imatinib mesylate (Bond et al., 2008), gefitinib (Brennan et al., 2014), trabectedin (Chuk et al., 2012), pirarubicin (Qi et al., 2012), ifosfamide (Choeyprasert et al., 2014; Li et al., 2014) and gemcitabine (Qi et al., 2012) have been investigated in pediatric and

Table 4. Hematologic and Non-hematologic Toxicities

Adverse event	Grade						Total	
	1 or 2		3		4			
	n	%	n	%	n	%	n	%
Anemia	5	27.8	0	0	0	0	5	27.8
Leucopenia	11	61.1	4	22.2	3	16.7	18	100
Thrombocytopenia	3	16.7	0	0	0	0	3	16.7
Nausea and vomiting	13	72.2	3	16.7	0	0	16	88.9
Fatigue	5	27.8	0	0	0	0	5	27.8
Alopecia	9	50	9	50	0	0	18	100
Impaired liver function	2	11.1	0	0	0	0	2	11.1
Impaired kidney function	0	0	0	0	0	0	0	0
Cardiotoxicity	0	0	0	0	0	0	0	0
Hematuresis	1	5.6	0	0	0	0	1	5.6

adult patients, but the response rate is low and survival time is short. As a result, we undertook this retrospective study to investigate the activity of continuous-infusion ifosfamide and doxorubicin combination as second-line therapy for patients with relapsing and refractory osteosarcoma.

Of the 18 patients available for response evaluation in this retrospective study, we found that the overall response rate and the tumor control rate for relapsing or refractory osteosarcoma were 0 and 22.3%, respectively. No patient achieved CR or PR, and four patients who achieved SD were all died from disease progression. At the cut-off date, the median OS was 9 months (rang: 3-29 months), and the median PFS was 2 months (rang: 2-5 months), which confirmed the poor prognosis of the disease.

Similar to other studies, the present study showed some grade 3-4 toxic events, such as leucopenia 7 (38.9%), nausea and vomiting 3 (16.7%) and alopecia 9 (50%), but these toxic events were resolved by using supportive treatments such as G-CSF, interleukin-11, and 5-HT3 receptor blockers (as antiemetics).

To our knowledge, our trial is the first study to assess the efficacy and safety of continuous-infusion ifosfamide as second-line chemotherapy in recurrent or refractory osteosarcoma. However, we also acknowledge that the present study was limited by its retrospective nature, the small number of patients, and possible patient selection bias. What's more, there were no guidelines to follow for the staging and timing of imaging evaluations in our institution. Despite these limitations, we conducted this study to explore a completely different strategy in a rare sarcoma for which there were no other therapeutic options. And our study suggested that the continuous-infusion ifosfamide and doxorubicin combination therapy were well tolerated and moderate effective, which could be considered as salvage therapy for patients with recurrent or refractory osteosarcoma. However, because of short follow-up time, we could not observe the long-term results of this combination therapy, which should be confirmed in future studies.

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