RESEARCH ARTICLE

# Ifosfamide-containing Regimens for Treating Patients with Osteosarcomas

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## Abstract

**Background: This systemic analysis was conducted to evaluate the efficacy and safety of an ifosfamide-containing regimen in treating patients with osteosarcoma. Methods: Clinical studies evaluating the efficacy and safety of Ifosfamide-containing regimen on response and safety for patients with osteosarcoma were identified by using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. Results: When ifosfamide-containing regimens were evaluated, 4 clinical studies which including 134 patients with osteosarcoma were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 44.8% (60/134) in ifosfamide-containing regimens. Major adverse effects were neutropenia, leukopenia, and fatigue inIfosfamide-containing regimens; No treatment related death occurred in cantharidin combined regimens. Conclusion: This systemic analysis suggests that ifosfamide-containing regimens are associated with good response rate and acceptable toxicity in treating patients with osteosarcoma, but this result should be confirmed by randomized clinical trials.**

**Keywords:** Ifosfamide - osteosarcoma - toxicity - adverse effects - response rate

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## Introduction

Osteosarcoma is one of the most common primary malignant tumor of bones, usually developed in adolescents with high malignant severity (Bao et al., 2013; He et al., 2013). Progress were made regarding overall survival for patients with recurrent or refractory osteosarcoma, but relapse is still reported among 30-40% of patients (Bramwell et al., 1992; Fuchs et al., 1998). Failure of standard treatment for patients with recurrent or refractory osteosarcoma is associated with a risk for poor prognosis. Thus, new regimens are needed for patients with recurrent or refractory osteosarcoma.

Ifosfamide may be used in the treatment of sarcoma given either as a single agent or in combination with doxorubicin (Sleijfer et al., 2010). The most commonly used regimen is three daily divided doses with doses ranging from 2 to 4 g/m$^2$/day given as an inpatient over 4 hours. Efforts have been made to increase the treatment effects of ifosfamide. Some evidence suggested that a more prolonged infusion may have an improved cytotoxicity and tolerability profile although it is associated with worse urothelial toxicity compared with the three day infusion (Lorigan et al., 2007). There is clinical investigation for the use of ifosfamide in combination with other chemotherapeutic agents, eg., cisplatin, epirubicin , methotrexate etc (Harris et al., 1995; Basaran et al., 2007; Zhao et al., 2010; Kudawara et al., 2013). However, the role of ifosfamide containing combination therapy in recurrent or refractory osteosarcoma has not bee well defined, and the results differed very much. The response rate of Zhao et al. was 46.9%, of Basaran et al. was 37%, of Harris et al. was 27%, and of Kudawara et al. was 66% (Harris et al., 1995; Basaran et al., 2007; Zhao et al., 2010; Kudawara et al., 2013).

With this background, we undertake this systemic study to analyze the efficacy and toxicity of ifosfamide containing therapy for recurrent or refractory osteosarcoma.

## Materials and Methods

*Search strategy*

We searched PUBMED, by using the following search term: (ifosfamide) and (osteosarcoma). All clinical studies evaluating the impact of ifosfamide on the response or survival and side effects for osteosarcoma published in English prior to October 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

*Inclusion and exclusion criteria*

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include

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published studies: (1) clinical studies, combined with docetaxel or pirarubicin; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced osteosarcoma, the presence of at least one bidimensionally measurable lesion, a performance status (WHO)2, age< 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

*Data collection and analysis*

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

## Results

There were 570 papers relevant to the search words (ifosfamide, osteosarcoma) by the end of October, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Harris et al., 1995; Basaran et al., 2007; Zhao et al., 2010; Kudawara et al., 2013) when ifosfamide was used in combination of chemotherapy. These studies had been carried out in China, Japan, Turkey and the United States. The following outcomes were presented in all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

When ifosfamide was used in combined chemotherapy with pirarubicin (epirubicine) or cisplatin, 4 studies included in this study are presented and the short-term outcomes suggested that the response rate of Zhao et al. was 46.9%, of Basaran et al. was 37%, of Harris et al. was 27%, and of Kudawara et al. was 66%. Totally, 134 patients were enrolled and 60 patients achieved CR or PR, the pooled response rate thus was 60/134 (44.8%). Observation on toxicities: major severe toxicities were hematologic toxicities, including Grade 3 or 4 anemia, leucopenia and thrombocytopenia in total cycles; mild toxicities included Grade 1 or 2 nausea and vomiting, fatigue and alopecia. There were no treatment-related deaths.

## Discussion

Patients with recurrent or refractory osteosarcoma have a very poor prognosis, and in this setting, combined chemotherapy was reported to be superior to the best supportive care in the management of patients with recurrent or refractory osteosarcoma (Cao et al., 2013; He et al., 2013; Chen et al., 2014; Diao et al., 2014; He et al., 2014). Various combination chemotherapy regimens as first-line treatment showed median response rates of 30-50%, and a median pro¬gression-free survival of 5-6 months (Jia et al., 2013; Jiang et al., 2013; Wang et al., 2013; Yang et al., 2013; Seker et al., 2014). In the passed several years, several clinical studies had been conducted to evaluate the efficacy of the ifosfamide containing regimens for patients with recurrent or refractory osteosarcoma. There is no standard second line treatment for these patients. Zhao and Yao assessed the therapeutic effect and adverse reactions to pirarubicin (THP) chemotherapy in osteosarcoma patients with lung metastasis, and analyzed the relationship between THP therapeutic effect and expression of *p*-glycoprotein and topoisomerase-II. Osteosarcoma patients with lung metastases at relapse were given THP and then cisplatin (DDP) or ifosfamide (IFO). Overall survival in patients receiving THP was 31.00 +/- 7.98 months, progression-free survival was 13.00 +/- 2.46 months. Objective response and partial response rates were 46.88% and 40.63%, respectively. There were no differences in overall survival and progression-free survival between the THP+DDP and THP+IFO regimens. Adverse reactions to THP chemotherapy were mainly gastrointestinal and myelosuppression. The therapeutic effect of THP was correlated with the expression of pglycoprotein and/or topoisomerase-II (Zhao et al., 2010). In another study, Basaran et al treated 45 patients with ifosfamide 2.0 g/m$^2$/day on days 2-4, cisplatin 100 mg/m$^2$ on day 1 and epirubicin 90 mg/m$^2$, repeated every 21 days. After six cycles of chemotherapy were administered (3 cycles prior to surgery and 3 cycles postoperatively), and with a median follow-up of 64, complete and good histological response to chemotherapy was 26 and 37%, respectively. The 5-year disease-free and overall survival rates were 41.9% and 48.2%. In this study, the most common grade 4 toxicity was neutropenia that occurred in 32% of patients (Basaran et al., 2007). In a study conducted in the USA, to compare the response rate among 33 patients with recurrent osteosarcoma. The comparison of response rate to ifosfamide was performed in patients younger than 30 years of age with previously untreated osteosarcoma with metastases at diagnosis and/or unresectable primary tumors (stratum 1) with that of patients with recurrent osteosarcoma following adjuvant chemotherapy who were not previously exposed to ifosfamide (stratum 2). Evaluation of response was conducted 3 weeks after two courses of ifosfamide (2400 mg/m$^2$ x 5 days). Nine of 33 (27%) evaluable patients in stratum 1 responded (1 complete and 8 partial responses) to ifosfamide. Among 30 evaluable patients in stratum 2, only 3 (10%) responded (1 complete and 2 partial responses; P = .04) Both groups of patients received equal doses of ifosfamide and experienced comparable toxicities. Results from this study suggest that the activity of new agents will be underestimated if tested in a population of heavily pretreated patients with recurrent disease. When possible, new chemotherapeutic agents should be tested in patients with a poor prognosis who have not been exposed to chemotherapy (Harris et al., 1995). From 1997 to 2003, Kudawara treated 40 patients (all <40 years of age) with non-metastatic osteosarcoma of the extremities. Two cycles of ifosfamide 1.5 g/m$^2$ plus cisplatin 120 mg/m$^2$ and doxorubicin 90 mg/m$^2$ were given as neoadjuvant

chemotherapy, and two cycles of doxorubicin/cisplatin and ifosfamide, and two cycles of high-dose methotrexate (10-12 g/m$^2$) were given post-operatively. All patients underwent limb salvage surgeries, and 66% showed good response to neoadjuvant chemotherapy. With a median follow-up period of 117 months, 31 of the evaluable 40 patients were continuously disease-free, 7 were currently alive with no evidence of disease, and 2 died of disease. There was no local recurrence. The 5-year event-free and overall survival rates were 83 and 98%, respectively. The 10-year event-free and overall survival rates were 80 and 95%, respectively. The major toxicity in this study was haematological (Kudawara et al., 2013). Several reasons might interpret the discrepancy of these studies: first, dosages of ifosfamide in these studies were different. Ifosfamide was given at a dose of 1.5 g/m$^2$ in Kudawara study, 2.4 g/m$^2$ in Harris study, and 2.0 g/m$^2$ in Basaran study; second, a possible patient selection bias might affect treatment results because of a small number of patients were included. Although some agents, e.g. epirubicin and ifosfamide have shown encouraging anti-tumor activity in patients with osteosarcoma, these regimens are inevitably accompanied by substantial toxicities, which reduce the value as a palliative treatment, especially in second line treatment for patients with relative poor clinical condition. Therefore, the need for new regimens with improved efficacy and safety is increasing for patients who have failed first line treatment. Ifosfamide. In this study, it is suggested that in ifosfamide based regimens 134 patients were enrolled and 60 patients achieved CR or PR, the pooled response rate thus was 60/134 (44.8%). Observation on toxicities: major severe toxicities were hematologic toxicities, including Grade 3 or 4 anemia, leucopenia and thrombocytopenia in total cycles; mild toxicities included Grade 1 or 2 nausea and vomiting, fatigue and alopecia. There were no treatment-related deaths.

However, the effective rate was not high, suggesting further studies, especially prospective clinical trials, focusing on treatments for patients with recurrent osteosarcoma should be strongly considered

In conclusion, this systemic analysis suggests that ifosfamide based regimens are associated with good activity with good tolerability in treating patients with recurrent or refractory osteosarcoma.

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