RESEARCH ARTICLE

# Gemcitabine for the Treatment of Patients with Osteosarcoma

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## Abstract

**Background: Patients with recurrent or refractory osteosarcoma are considered to have a very poor prognosis, and new regimens are needed to improve the prognosis in this setting. Gemcitabine, a nucleoside antimetabolite, is an analog of deoxycytidine which mainly inhibits DNA synthesis through interfering with DNA chain elongation and depleting deoxynucleotide stores, resulting in gemcitabine-induced cell death. Here we performed a systemic analysis to evaluate gemcitabine based chemotherapy as salvage treatment for patients with recurrent or refractory osteosarcoma. Methods: Clinical studies evaluating the impact of gemcitabine based regimens on response and safety for patients with osteosarcoma were identified by using a predefined search strategy. Pooled response rates (RRs) of treatment were calculated. Results: In gemcitabine based regimens, 4 clinical studies which included 66 patients with recurrent or refractory osteosarcoma were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 12.1% (8/66) in gemcitabine based regimens. Major adverse effects were hematologic toxicity, including grade 3 or 4 anemia, leucopenia and thrombocytopenia in gemcitabine based treatment. No treatment related death occurred in gemcitabine based treatment. Conclusion: This systemic analysis suggests that gemcitabine based regimens are associated with mild activity with good tolerability in treating patients with recurrent or refractory osteosarcoma.**

**Keywords:** Osteosarcoma - gemcitabine

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## Introduction

Osteosarcoma is the most common malignant primary bone tumor (Nagarajan et al., 2003). 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.

Gemcitabine, a nucleoside antimetabolite, is an analog of deoxycytidine which mainly inhibits DNA synthesis through interfering with DNA chain elongation and depleting deoxynucleotide stores, resulting in gemcitabine-induced cell death (Gandhi et al., 1996). Docetaxel is a semisynthetic analog of paclitaxel, which promotes microtubule assembly and inhibits disassembly resulting in cell cycle arrest and apoptosis (Ringel et al., 1991). In vitro study, synergistic antitumor activity of the combination of docetaxel and gemcitabine has been observed in several different cell lines, including osteosarcoma cell lines (Leu et al., 2004; Ricotti et al., 2003). Recently, several retrospective clinical studies had been conducted to assess the efficacy and toxicity of gemcitabine-docetaxel combination therapy for sarcomas, but the results were controversial (Mora et al., 2009; Ebeling et al., 2008). Therefore, the role of gemcitabine containing combination therapy in recurrent or refractory osteosarcoma is still not well defined. With this background, we undertake this systemic study to assess the efficacy and toxicity of gemcitabine containing therapy for recurrent or refractory osteosarcoma.

## Materials and Methods

*Search strategy*

We searched PUBMED, by using the following search term: (gemcitabine) and (osteosarcoma). All clinical studies evaluating the impact of gemcitabine on the response or survival and side effects for osteosarcoma published in English prior to July 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 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

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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 66 papers relevant to the search words by the end of June, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Fox et al., 2012; Qi et al., 2012; He et al., 2013; Song et al., 2014) when gemcitabine was used in combination of chemotherapy. These studies had been carried out in China, Korea, and the United States. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

When gemcitabine was used in combined chemotherapy with docetaxel or pirarubicin, 4 studies included in this study are presented and the short-term outcomes suggested that the response rate of Song et al. was 23.5%, of He et al. was 13%, of Qi et al. was 5.6%, and of Fox et al. was 7.1%. Totally, 66 patients were enrolled and 8 patients achieved CR or PR, the pooled response rate thus was 8/66 (12.1%). 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 man-agement 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; Seker et al., 2014; Wang et al., 2013; Yang et al., 2013). In the passed several years, several clinical studies had been conducted to evaluate the efficacy of the gemcitabine containing regimens for patients with recurrent or refractory osteosarcoma. There is no standard second line treatment for these patients. McTiernan and Whelan (McTiernan et al., 2004) reported that single-agent docetaxel was inactive in patients with relapsed osteosarcoma, and Mora et al. (2009) reported that the gemcitabine-docetaxel regimen showed antitumor activity against Ewing sarcoma but not osteosarcoma, while Navid et al. (2008) did a retrospective study to find that gemcitabine-docetaxel combination therapy was well tolerated and showed antitumor activity in children and adolescents with recurrent or refractory osteosarcoma, with an overall response rate of 30% and a disease control rate of 40%. In another conducted in China, it is reported that the response rate was 25.0 % in patients who received pirarubicin-based chemotherapy, while it was 13.0 % in the gemcitabine-docetaxel group. Moreover, the median OS was longer in the pirarubicin-based chemotherapy group (14.0 vs. 9.0 months, $P < 0.05$), especially in the pirarubicin-ifosfamide (14.0 months) and pirarubicin-cisplatin (15.0 months) subgroups. The incidence of grade 3-4 neutropenia was higher in the gemcitabine-docetaxel group (5.8 vs. 43.5 %, $P < 0.05$); other grade 3-4 toxicities were comparable in the two groups (He et al., 2013). He et al., suggested that pirarubicin-based chemotherapy was comparable with gemcitabine-docetaxel as a second-line treatment for relapsed and refractory osteosarcoma, and it even seemed to show greater efficacy, with milder toxicity (He et al., 2013). In another study, Qi et al treated 18 patients with gemcitabine at 675 mg/m$^2$ on days 1 and 8, and docetaxel at 75-100 mg/m$^2$ on Day 8, after a total of 44 cycles of chemotherapy (median: 2 courses), the overall response rate was 5.6% and the disease control rate was 22.3%, with one partial response and three patients with stable disease. The median time to progression and overall survival time were 2 months (range: 2-6 months) and 8 months (range: 3-21 months), respectively (Qi et al., 2012). They fond In this study, gemcitabine-docetaxel combination therapy was well tolerated and marginally effective, which could be considered as salvage therapy for patients with recurrent or refractory high-grade osteosarcoma (Qi et al., 2012). But patients achieved benefits from the combination regimen of gemcitabine and docetaxel was small compared with the efficacy reported by Navid et al. (Navid et al., 2008). In a study conducted in the USA, it was reported that among 14 patients with recurrent osteosarcoma, only 1 partial response was observed (Fox et al., 2012). Several reasons might interpret the discrepancy of these studies: first, dosages of gemcitabine and docetaxel in most studies were lower than those used in adult patients, gemcitabine was given at a dose of 675 mg/m$^2$ which was in the lowest range and the dose of docetaxel was also lower than that reported in adult studies; second, a possible patient selection bias might affect treatment results because of a small number of patients were included; lastly, 50% of the patients in the study of Qi et al. had a local and distant failure after primary therapy, which was higher than 19% of the patients in Navid's study (Qi et al., 2012).

Although some agents, e.g. epirubicin and ifosfamide have shown encouraging anti-tumor activity in patients with osteosarcoma, these regimens are inevitably

accom¬panied 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. Gemcitabine, a nucleoside antimetabolite, is an analog of deoxycytidine which mainly inhibits DNA synthesis through interfering with DNA chain elongation and depleting deoxynucleotide stores, resulting in gemcitabine-induced cell death, and clinical side effects are generally mild. Thus, we performed this systemic analysis to evaluate gemcitabine based chemotherapy as salvage treatment for patients with recurrent or refractory osteosarcoma. In this study, it is suggested that, in all patients, pooled RR was 12.1% (8/66) in gemcitabine based regimens. Major adverse effects were hematologic toxicities, including grade 3 or 4 anemia, leucopenia and thrombocytopenia in gemcitabine based treatment. No treatment related death occurred in gemcitabine based treatment. 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 gemcitabine based regimens are associated with mild active with good tolerability in treating patients with recurrent or refractory osteosarcoma.

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