RESEARCH ARTICLE

Gemcitabine in Treating Patients with Refractory or Relapsed Multiple Myeloma

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Abstract

Background: Patients with refractory or relapsed multiple myeloma are considered to have a very poor prognosis, and new regimens are needed to improve the outcome. 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 refractory and relapsed multiple myeloma. Methods: Clinical studies evaluating the impact of gemcitabine based regimens on response and safety for patients with refractory and relapsed multiple myeloma were identified by using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. Results: In gemcitabine based regimens, 3 clinical studies which including 57 patients with refractory and relapsed multiple myeloma were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 15.7% (9/57) in gemcitabine based regimens. Major adverse effects were hematologic toxicity, including grade 3 or 4 anemia, leucopenia and thrombocytopenia i. No treatment related death occurred with gemcitabine based treatment. Conclusion: This systemic analysis suggests that gemcitabine based regimens are associated with mild activity with good tolerability in treating patients with refractory or relapsed multiple myeloma.

Keywords: Multiple myeloma - relapsed/refractory cases - chemotherapy - gemcitabine

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Introduction

Standard regimens for the treatment of multiple myeloma comprise alkylating agents, vincristine, adriamycin, methylprednisolone and dexamethasone. Steroids were suggested to make the major contribution to anti-tumor effects in refractory myeloma when applied together with anthracyclines and/or vincristine (e.g., in the VAD protocol) (Barlogie et al., 1984). Although high-dose chemotherapy followed by stem cell support may be effective and even superior to standard-dose chemotherapy (Fernand et al., 1989), the majority of myeloma patients will either not qualify for these cytotoxic protocols or not be definitely cured by this procedure (Attal et al., 1995). In addition, without inducing remission by conventional treatment is the single most important adverse predictor of outcome (Björkstrand et al., 1995). For these reasons, there is an urgent need to develop a new efficient cytotoxic regimen to treat patients with refractory myeloma.

Gemcitabine is used in clinical settings for the treatment of slowly proliferating tumors, e.g. head and neck cancer (Braakhuis et al., 1991), colorectal cancer (Moore et al., 1992) and non-small cell lung cancer (Lilenbaum et al., 1993). However, no large clinical trial was published to demonstrate the efficacy of gemcitabine in multiple myeloma. On this background, we report a pooled analysis on gemcitabine in treating patients with refractory or relapsed multiple myeloma.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (refractory and relapsed multiple myeloma) and (Gemcitabine). All clinical studies evaluating the impact of gemcitabine on the response or survival and side effects for colon cancer published in English prior to July 2014 were identified. If samples of two studies overlap, only the newest 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 paclitaxel or cisplatin; (2) The study was performed in

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accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified refractory and relapsed multiple myeloma, 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. Outcome measures presented in at least 3 studies were extracted for combined analysis.

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, 3 studies were identified (Gazitt et al., 2006; Offidani et al., 2002; Weick et al., 2002) 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, 3 studies included in this study are presented and the short-term outcomes suggested that the response rate of Gazitt et al. was 33.3%, of Offidani et al. was 31.3%, and of Weick et al. was 0%. Totally, 57 patients were enrolled and 9 patients achieved CR or PR, the pooled response rate thus was 9/57 (16%). Observation on toxicities: No grade 4 hematological toxicity was seen after gemcitabine treatment, whereas > or = 3 grade toxicities including neutropenia and thrombocytopenia, respectively. There were no treatment-related deaths.

Discussion

Multiple myeloma (MM) is a plasma cell neoplasm in the bone marrow and is likely to present with hypercalcemia, renal failure, anemia, bone resorption, and/or immunodeficiency (Kyle e al., 2003). Treatment approaches in the management of MM have made a remarkable progress in the recent decades and are comprised of high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation and novel therapies using proteasome inhibitors and immunomodulatory drugs (Kumar e al., 2008; Gay et al., 2011). These strategies have improved overall survival of MM patients. However, most patients eventually relapse even after the achievement of complete response (Palumbo et al., 2011). Therefore, other novel therapeutic approaches are strongly needed to further improve the outcome of MM.

Gemcitabine, a cytosine arabinoside analogue, is a pyrimidine nucleoside with known antitumor activity against solid tumour malignancies and hematological malignancies, and is widely used by clinical oncologist in China (Su et al., 2013; Sun et al., 2013; Wang et al., 2013; Wei et al., 2013; Yuan et al., 2013). In vitro, the rationale for using gemcitabine in MM is its ability to induce apoptosis in myeloma cell lines1 and block these cells in the cell cycle S-phase whatever the level of bcl-2 or Il-6 expression.2 Preliminary reports showed promising results in recurrent MM patients. Offidani evaluated the activity of gemcitabine as a single agent and combining it with cisplatin in relapsed-refractory MM. In this study, 16 patients with advanced MM received intravenous gemcitabine 1250 mg/mq (days 1, 8 and 15) as a single agent for a total of 3 monthly courses. The responders received another three courses, and the non-responders received three courses of gemcitabine 1000 mg/mq (days 1, 8 and 15) plus cisplatin 80 mg/mq (day 1). No grade 4 hematological toxicity was seen after gemcitabine treatment, whereas > or = 3 grade neutropenia and thrombocytopenia were seen in 21 and 13% of the gemcitabine-cisplatin infusions, respectively. Non-hematological toxicity was negligible for both the regimens. After three courses of gemcitabine as a single agent, the response rate was 31% (1 complete response, 1 partial response and 3 minimal response). Eight patients (50%) achieved stable disease and 3 (19%) had disease progression. Ten patients received gemcitabine-cisplatin and were evaluable for the response. Two patients progressed, four maintained stable disease whereas four patients, unresponsive to gemcitabine, obtained a response (3 partial response and 1 minimal response) (Offidani et al., 2002) Weick et al. have reported a lack of objective responses but stable disease in 57% of the patients and a median survival of 8 months. The grade 3-4 neutropenia and/or thrombocytopenia were 31 and 51% of the patients, respectively, without major extra-hematological toxicity (Weick et al., 2002). Gazitt et al. initiated a phase II clinical trial of paclitaxel 150 mg/m (2) IV over 3 h followed by gemcitabine 3000 mg/m (2) IV over 30-60 min in patients with relapsed or refractory MM. In this study, the regimen was administered every two weeks for a total of six cycles. Twelve patients enrolled, 3 discontinued treatment after 1 or 2 cycles because of severe neutropenia. Then, the protocol was modified to reduce the starting dose of gemcitabine to 2,000 mg/m (2). This resulted in tolerable hematological and mild non-hematological toxicities in the rest of the patients. According to the the result, one patient died before the onset of treatment. Of the 8 remaining patients treated with a reduced dose of gemcitabine, 1 achieved a durable CR, 3 had PR, 1 had minor response (MR), 1 had stable disease and 2 had progressive disease. The CR patient had a 98% reduction in the M-protein, beta2-microglobulin and plasma cells (Gazitt et al., 2006).

In our systemic analysis, we screened the title and read the abstract from Pubmed, 3 studies were identified when gemcitabine was used in combination of chemotherapy.

When gemcitabine was used in combined chemotherapy with docetaxel or pirarubicin, 3 studies included in this study are presented and the short-term outcomes suggested that the response rate of Gazitt et al. was 33.3%, of Offidani et al. was 31.3%, and of Weick et al. was 0%. Totally, 57 patients were enrolled and 9 patients achieved CR or PR, the pooled response rate thus was 9/57 (16%). Regardiing toxicities, few grade 4 hematological toxicity was seen after gemcitabine treatment, whereas > or = 3 grade toxicities including neutropenia and thrombocytopenia, respectively. There were no treatment-related deaths.

In conclusion, our systemic analysis suggests that gemcitabine based regimens are associated with mild activity with good tolerability in treating patients with refractory or relapsed multiple myeloma

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