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, leukopenia and thrombocytopenia. 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
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 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%). Regarding 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

References

Attal M, Harousseau JL, Stoppa AM, et al (1995). Hidhose chemotherapy in multiple myeloma: a prospective randomized study of the “Intergroupe Français du Myelome” (IFM). Vth International Workshop on Multiple Myeloma 1995, La Baule, France.

Barlogie B, Smith L, Alexanian R (1984). Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med, 310, 1353-6.

Fernand JP, Levy Y, Gerota J, et al (1989). Treatment of aggressive multiple myeloma by high-dose chemotherapy and total body irradiation followed by blood stem cells autologous graft. Blood, 73, 20-3.

Björkstrand B (1995). 474 autotransplants in multiple myeloma—results of the EBMT. Vth International Workshop on Multiple Myeloma 1995; September 10-13: La Baule, France.

Braakhuis BJ, van Dongen GA, Vermorken JB, et al (1991). Preclinical in vivo activity of 2’, 2’-difluorodeoxycytidine (gemcitabine) against human head and neck cancer. Cancer Res, 51, 211-4.

Gazitt Y1, Shaughnessy P, Rothenberg ML, et al (2006). A phase II trial with gemcitabine and paclitaxel for the treatment of refractory and relapsed multiple myeloma patients. Oncol Rep, 16, 877-84.

Gay F, Larocca A, Wijermans P, et al (2011). Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: Analysis of 1175 patients. Blood, 117, 3025-31.

Kumar SK, Rajkumar SV, Dispenzieri A, et al (2008). Improved survival in multiple myeloma and the impact of novel therapies. Blood, 111, 2516-20.

Kyle RA, Child JA, Anderson K, et al (2003). Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol, 121, 749-57.

Lilenbaum RC, Green MR (1993). Novel chemotherapeutic agents in the treatment of non-small-cell lung cancer. J Clin Oncol, 11, 1391-402.

Moore DF Jr, Pazdur R, Daugherty K et al (1992). Phase II study of gemcitabine in advanced colorectal adenocarcinoma. Invest New Drugs, 10, 323-5.

Offidani M, Mele A, Corvatta L, Marconi M et al (2002). Gemcitabine alone or combined with cisplatin in relapsed or refractory multiple myeloma. Leuk Lymphoma, 43, 1273-9.

Palumbo A, Anderson K (2011). Multiple myeloma. New Engl J Med, 364, 1046-60.

Sun TT, Wang JL, Fang JY (2013). Gemcitabine alone or in combination with cisplatin for advanced biliary tract carcinomas: an overview of clinical evidence. Asian Pac J Cancer Prev, 14, 877-83.

Su A, Zhang J, Pan ZH, et al (2013). Salvage therapy of gemcitabine plus endostar significantly improves progression-free survival (PFS) with platinum-resistant recurrent epithelial ovarian cancer. Asian Pac J Cancer Prev, 14, 1841-6.

Wang M, Gu J, Wang HX, et al (2012). Retrospective study of gemcitabine based chemotherapy for unresectable or recurrent esophagus squamous cell carcinoma refractory to first line chemotherapy. Asian Pac J Cancer Prev, 13, 4153-6.

Weii MY, Zhuang YF, Wang WM (2014). Gemcitabine for the treatment of patients with osteosarcoma. Asian Pac J Cancer Prev, 15, 7159-62.

Weick JK1, Crowley JJ, Hussein MA, et al (2002). The evaluation of gemcitabine in resistant or relapsing multiple myeloma, phase II: a Southwest Oncology Group study. Invest New Drug, 20, 117-21.

Yuan SF, Zhang LP, Zhu LJ, et al (2013). Phase II clinical study on the GEMOX regimen as second-line therapy for advanced ovarian cancer. Asian Pac J Cancer Prev, 14, 3949-53.