

Evaluation of gemcitabine in relapsed or refractory multiple myeloma

Haematologica 2004; 89:(10)e125

Gemcitabine, a cytosine arabinoside analogue, is a pyrimidine nucleoside with known antitumor activity against solid tumour malignancies and hematological malignancies. *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 Bcl-6 expression.² Preliminary reports showed promising results in recurrent multiple myeloma (MM) patients. Offidani and his group reported a 31% response rate and 50% of stable disease, a negligible non-hematological toxicity, no grade 4 hematological toxicity and a median time to treatment failure of 8 months.³ 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.⁴ Because of these conflicting results, we conducted a multicentric phase II study in order to evaluate the single-agent gemcitabine activity in thirteen patients with relapsed or refractory MM. This protocol was approved by the Centre Léon Bérard Ethics Committee and all the patients gave written informed consent. Intravenous gemcitabine 1000 mg/m² was administered as a 30 minutes infusion on days one and eight, every three weeks, for a maximum of 6 courses.

The median age at diagnosis was 61 years (range, 26-80) and the M/F ratio 2.25. Nine patients had an IgG, three patients an IgA and one patient a light-chain M-component. Ten patients (72%) were stage III at diagnosis. None of them had received autologous stem cell transplantation. Four patients (31%) were primary refractory to standard treatment, 3 relapsed and six patients were secondary refractory. The median treatment courses before gemcitabine was 4 (range, 1-5). Ten patients (77%) had progressed after thalidomide alone or in combination. The median time from diagnosis to the first course of gemcitabine was 55 months (range, 8-120). The patients received a median of 3 gemcitabine cycles (range, 1-6). Three patients completed 6 courses of treatment, 6 patients stopped because of progressive disease and 4 patients because of toxicity. The median total dose

received was 6,000 mg/m² (range 1,000-12,000), but only 3,000 mg/m² in patients with renal failure at diagnosis.

The overall response rate in 13 evaluable patients was 2/13 (15%), consisting of one partial response and one minor response. Both these patients were previously in relapse from at least four treatment courses. Two patients had stable disease. The median time to progression for the responders and the stable patients was 7.5 months (range, 5-22). With a median follow-up of 20 months, four patients (31%) were alive at the time of evaluation. The median survival from onset of gemcitabine was 14 months (range, 2-31). Toxicity was mainly hematological with 42% of the patients developing grade III/IV neutropenia, requiring the administration of growth factors. Eight (57%) patients had grade III/IV thrombopenia. There were no toxic deaths.

Our results suggest that a single agent gemcitabine possesses modest activity in heavily pretreated relapsed or refractory MM, with an acceptable toxicity profile. Future trials should study combinations of gemcitabine with other compounds, such as dexamethasone, thalidomide or bortezomib.

Xavier Leleu,¹ Jacques Troncy,² Fadela Bouafia,³ Mauricette Michallet,²

Thierry Facon,¹ Charles Dumontet³

¹Service des Maladies du Sang, CHU, Lille; ²Service d'Hématologie, HEH, Lyon; ³Service d'Hématologie, CHLS, Lyon

Correspondence: Xavier Leleu

Service des Maladies du Sang, CHU, Lille

Phone: 33.(0).3.20.44.57.13 Fax: 33.(0).3.20.44.47.08

E-mail: x-leleu@chru-lille.fr

References

1. Nabhan C, Gajria D, Krett NL, Gandhi V, Ghias K, Rosen ST. Caspase activation is required for gemcitabine activity in multiple myeloma cell lines. *Mol Cancer Ther* 2002; 1:1221-7.
2. Gazitt Y, Rothenberg ML, Hilsenbeck SG, Fey V, Thomas C, Montegomrey W. Bcl-2 overexpression is associated with resistance to paclitaxel, but not gemcitabine, in multiple myeloma cells. *Int J Oncol* 1998; 13:839-48.
3. Offidani M, Mele A, Corvatta L, et al. Gemcitabine alone or combined with cisplatin in relapsed or refractory multiple myeloma. *Leuk Lymphoma* 2002; 43:1273-9.
4. Weick JK, Crowley JJ, Hussein MA, Moore DE, Barlogie B. The evaluation of gemcitabine in resistant or relapsing multiple myeloma, phase II: a Southwest Oncology Group study. *Invest New Drugs* 2002; 20:117-21.