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Phase II study of gemcitabine in previously platinum-treated ovarian cancer patients

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Fifty-one patients with histologically confirmed epithelial stage III or IV ovarian cancer were entered into a study in which gemcitabine 800 mg/m^2 was given as a 30 min intravenous infusion in a cycle once a week for 3 weeks followed by a week of rest. Patients were aged 58 years (range 23–70 years) with WHO performance status 0–2, and had received up to two different chemotherapy regimens. Thirty-eight patients had received only one prior platinum-containing chemotherapy regimen whereas 9 had received a first-line regimen on more than one occasion. A further 3 patients had received two different regimens. Of 42 patients evaluable for response, 8 (19%; 95% CI: 9%–34%) were partial responders. Seven of the 8 responders were resistant to first-line platinum-based therapy. Median duration of response was 8.1 months (range 4.4–12.5 months). Median progression-free survival was 2.8 months (range 0.2–12.5 months). Haematological toxicity with gemcitabine was modest, with grade 3 leukopenia (11 patients) and grades 3 and 4 thrombocytopenia (6 patients). Grade 3 non-haematological toxicity included nausea/vomiting (6 patients) and elevated AST/ALT (1 patient), while dose-limiting non-haematologic toxicity consisted of flu-like symptoms (2 patients), peripheral oedema (1 patient) and lethargy (1 patient). The activity and modest haematological and non-haematological toxicity seen with gemcitabine suggest that this agent should be further evaluated in the treatment of patients with ovarian cancer and in combination chemotherapy regimens, primarily in combination with platinum.

Introduction

More than half of all patients with ovarian cancer present with advanced disease at the time of diagnosis. A number of cytostatic drugs are known to be active against ovarian cancer, but the majority of patients eventually die of their disease. Platinum analogues with cyclophosphamide or paclitaxel are currently the most active drugs in the chemotherapy of ovarian cancer. Further progress in the treatment of this disease may be obtained by the development of new drugs which are active in patients with platinum-resistant ovarian tumours. The novel nucleoside analogue gemcitabine is an agent with promise in ovarian cancer. In an early small phase II study, 2 of 7 eligible ovarian cancer patients responded to gemcitabine.[1] We therefore performed a phase II trial with gemcitabine in previously platinum-treated ovarian cancer patients.[2]

Patients and methods

To be included in the study patients had to have histologically confirmed epithelial ovarian carcinoma. They had to have received standard chemotherapy, but no more than two different chemotherapy regimens. Furthermore, a performance status of 0–2 (WHO) and measurable disease were required.

Gemcitabine was given as an intravenous infusion over 30 min at a dose of 800 mg/m^2 on days 1, 8 and 15 every 28 days. To be evaluable for response, at least two courses had to be given. The actual dose administered was reduced or escalated according to the actual white blood cell counts and/or the platelet counts. Skin toxicity grade 2 or other non-haematological toxicity grade 3 allowed dose reduction to 50%.

Results

A total of 51 patients entered the study and 50 were eligible. Protocol violations were registered in 3 cases. Forty-two patients were evaluable for

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Table 1. Prior treatment and prior response rates in 50 eligible patients

Treatments	1 regimen	38 patients
	1 regimen × 2	6 patients
	1 regimen × 3	2 patients
	1 regimen × 4	1 patient
	2 regimens	3 patients
Responses	CR: 10 patients	(20%)
	PR: 19 patients	(38%)

CR = Complete response; PR = partial response.

response and 48 were evaluable for toxicity. All 50 patients were classified in stage III (21 patients) or stage IV (29 patients). The median age at inclusion into the study was 58 years (range 23–70 years).

Thirty-eight patients had received only one prior platinum-containing chemotherapy regimen (Table 1). In 9 patients the first-line therapy had been repeated on more than one occasion, while only 3 patients had been treated with 2 different regimens. The combined response rate (CR + PR) to these prior treatments was 58% (Table 1).

The median number of courses with gemcitabine treatment was 3 courses (range 0–13) and a total of 181 courses were given. The standard dose was reduced or omitted for 32% and 8% of injections, was escalated for 9% of injections, and was given as assigned for 51% of injections.

Among 42 patients evaluable for response, 8 (19%; 95% CI: 9%–34%) responded with a partial remission. The median duration of the responses was 8.1 months (range 4.4–12.5 months). Median progression-free survival was 2.8 months (range 0.2–12.5 months). Five of the 8 gemcitabine responders had stage IV disease. In all, 7 of the 8 responders to gemcitabine were resistant to first-line platinum-based therapy. Three responders were resistant to prior first-line therapy of cyclophosphamide and cisplatin (CP) and 1 to carboplatin and cyclophosphamide (CpC). Another 3 responders to gemcitabine had achieved a PR on first-line therapy (1 CP, 1 CpC and 1 cisplatin plus etoposide), but progressed again during this therapy. The last responder had achieved a complete remission on CP, once again on CpC, but failed the second time CpC was applied.

The haematological toxicity with gemcitabine was modest, with grade 3 leukopenia in 11 patients and grades 3 and 4 thrombocytopenia in 5 and 1 patients respectively. Non-haematological toxicity grade 3 was nausea/vomiting in 6 patients and elevated AST/ALT in 1 patient, while dose-limiting non-haematological toxicity consisted of flu-like symptoms in 2 patients, peripheral oedema in 1 patient and lethargy in 1 patient.

Discussion

In this study, gemcitabine was found to be active in patients with ovarian cancer previously treated with combination chemotherapy including platinum-based agents. One of the important features of the gemcitabine trial is that many of the responding patients had poor prognostic characteristics. Notably, 7 of 8 responding patients (88%) were found to be resistant to first-line platinum-based therapy and 5 of the 8 responding patients had stage IV disease. These results with gemcitabine were obtained with only modest haematological and non-haematological toxicity. The toxicity profile of gemcitabine is in marked contrast with that of some of the other new agents under study in ovarian cancer. Therefore, according to the results of this study, gemcitabine should be further evaluated in the treatment of patients with ovarian cancer. If the activity of gemcitabine is confirmed in other and more extended phase II studies, gemcitabine should be tested in combination chemotherapy regimens, primarily in combination with platinum agents.

References

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