A phase II study of gemcitabine in platinum pre-treated patients with advanced epithelial ovarian cancer

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Summary

Background: Most patients with advanced ovarian cancer will relapse following platinum-based combination chemotherapy and be considered for second-line treatment. Gemcitabine, a nucleoside analogue, is active against a range of solid tumors. This phase II study investigated the activity of single-agent gemcitabine in patients with recurrent ovarian cancer.

Patients and methods: Thirty-eight patients with FIGO stage III (34%) or IV (64%) ovarian cancer who were previously treated with platinum-containing regimens were enrolled. Patients received 1200 mg/m² gemcitabine on days 1, 8 and 15 of a 28-day cycle.

Results: Patients completed an average of 3.6 cycles. Two complete and three partial responses were seen in 36 evaluable patients, for an overall response rate of 13.9% (95% CI: 4.7%–29.5%). The median survival time was 6.7 months. Toxicities were generally mild. The most common were grade 3–4 neutropenia and grade 3 leukopenia reported in 23.7% and 10.5% of patients, respectively. One patient had grade 4 pulmonary toxicity.

Conclusion: Single-agent gemcitabine is active and well tolerated in patients with recurrent ovarian cancer.

Key words: gemcitabine, ovarian cancer, phase II, single agent

Introduction

Ovarian cancer is the fourth leading cause of death in women [1]. The majority of women are diagnosed with advanced stage tumors and, despite an aggressive approach to treatment with debulking surgery and platinum-based combination chemotherapy, most patients will relapse and be considered for second-line treatment. The primary objective of treatment in patients with recurrent ovarian cancer is palliation and making quality of life an important endpoint. There is a clear need for treatment in this group of patients that is of potential benefit in reducing tumor related symptoms and not associated with unacceptable toxicity.

Gemcitabine is a novel nucleoside analogue with a broad spectrum of activity against a range of solid tumors, including non-small cell lung cancer (NSCLC) [2–4], bladder [5], pancreas [6] and breast cancers [7]. Lund et al. initially reported a 19% response with weekly doses of 800 mg/m² gemcitabine treatment in patients with recurrent ovarian cancer considered to have a poor prognosis (platinum refractory and/or bulky disease) [8]. In a subsequent study using 1250 mg/m² gemcitabine in platinum-resistant patients who had relapsed within months of platinum therapy, Neijt et al. reported a 22% response rate and a tolerable toxicity profile [9]. The purpose of this phase II study was to evaluate the clinical activity and toxicity of gemcitabine in women with relapsed ovarian cancer, whose sole prior treatment was platinum-based chemotherapy.

Patients and methods

Between December 1993 and March 1995, 38 female patients were enrolled in three countries, France, Australia and Spain (8 centres). Patients had to have recurrent or advanced FIGO stage III or IV epithelial ovarian cancer, prior treatment with one platinum-based regimen, a Karnofsky performance status (KPS) of 60 or more, estimated life expectancy of at least 12 weeks, and adequate bone marrow reserve.

Single-agent, 1200 mg/m² gemcitabine was given intravenously over 30 minutes on days 1, 8 and 15 of a 28-day cycle. Treatment was continued for a maximum of 8 cycles from time of best response, or until discontinuation of treatment at investigator or patient discretion.

Efficacy assessments before each gemcitabine dose were weight, use of analgesia, and performance status; and before each treatment cycle were patient serum CA125, a limited medical examination including tumor measurement of lesions, and quality of life (EORTC QLQ-C30 questionnaire) [10].

Results

All 38 patients were treated previously with at least one platinum-containing regimen and four received prior
patients required transfusions. One patient died from disease was documented in 50% of patients. The median and grade 3 leukopenia in 10.5% of patients. Grade 3-4 anemia was observed in 10.5% of patients and eight responders. The overall response rate, including CA 125 (col), 60 were reduced and 20 were omitted. Leukopenia caused most dose reductions (47%) and omissions (25%), followed by thrombocytopenia (30% and 25%, respectively).

Of the 36 evaluable patients, two had a complete response and three had a partial response, for an overall response rate of 13.9% (95% CI: 4.7%-29.5%). Stable disease was documented in 50% of patients. The median survival time for all patients was 6.7 months (95% CI: 5.5-8.4 months), the median time to partial response was 1.8 months (95% CI: 1.0-1.9 months), and the median duration of response was 10.6 months (95% CI: 3.3-14.0 months). Four patients were considered CA 125 responders. The overall response rate, including CA 125 responses was 23%.

Hematologic and nonhematologic toxicities were mild. The most severe were WHO grades 3 and 4 neutropenia seen in 21.1% and 2.6% of patients, respectively, and grade 3 leukopenia in 10.5% of patients. Grade 3-4 anemia was observed in 10.5% of patients and eight patients required transfusions. One patient died from septic shock (Candida albicans septicemia) that was not related to gemcitabine treatment. Grade 3 nausea/vomiting occurred in 5.3% of patients. Grade 1–2 fever, which was generally transient and rarely had clinical consequences, was reported in 26% of patients. One patient had grade 3 alopecia, but over 92% of patients reported no hair loss. Pulmonary toxicity was reported in one patient (grade 3) with severe dyspnea and another patient (grade 4) with lung fibrosis. Liver and kidney function were unaffected in the majority of patients.

For the quality of life evaluation, no significant differences (P < 0.05) were noted in changes from baseline mean scores except for improvement in the emotional functioning scale after cycles 1 and 2 and worsening of nausea and vomiting after cycle 2.

**Discussion**

The optimum treatment for women with recurrent ovarian cancer following initial platinum-based chemotherapy is unclear. While there are a number of drugs [11-15] with demonstrable activity, objective response rates are generally below 20% with duration of response measured in months. In this study, gemcitabine produced an overall response rate of 13.9% (95% CI: 4.7%-29.5%), which is consistent with response rates observed in other phase II studies of gemcitabine in patients with recurrent ovarian cancer (13-22%) [8, 9] and comparable with other palliative chemotherapy results. Tumor size and platinum free interval are recognised prognostic factors in patients with recurrent ovarian cancer. Twelve patients had tumors of greater than 5 cm diameter and, of these, one had a partial response and seven had stable disease. Time to platinum failure ranged from one to 25 months, with 22 patients (58%) having a platinum failure of six months or less. Patients having had a short interval between cisplatin failure and gemcitabine treatment might be expected to have a poor response, but there were two partial responders and nine patients with stable disease whose time to treatment failure was six months or less. One patient with a partial response progressed while on platinum treatment, and received gemcitabine one month after platinum therapy was discontinued. However, patients with a long interval between ending platinum treatment and beginning gemcitabine treatment had the best response to gemcitabine.

CA 125 levels are often elevated in patients with ovarian cancer and are commonly used to evaluate response and make treatment decisions in practice. The discrepancy between the response rate including the CA125 response (23%) and the objective tumour response rate (13.9%) highlights the problems associated with assessment of objective response in women with recurrent ovarian cancer.

Gemcitabine was well tolerated with uncomplicated neutropenia, the primary hematologic toxicity. Non-hematologic toxicities were generally mild in keeping with toxicities observed in other phase II studies of gemcita-
bine in this setting [8, 9]. The low number of doses omitted or reduced also attested to the acceptability and good tolerance of treatment making it a suitable agent for palliative treatment in patients with recurrent ovarian cancer.

References


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