Efficacy of gemcitabine in heavily pretreated advanced ovarian cancer patients

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Summary

Single agent gemcitabine was used in recurrent epithelial ovarian cancer patients after standard treatment with debulking surgery and platin-paclitaxel based chemotherapy. Response rates and toxicity results were evaluated retrospectively. Gemcitabine was given in 1000 mg/m^2 intravenous infusion over 30 minutes at 1, 8, 15 days of every 28 days. Clinical response was evaluated with clinical findings, serum CA 125 levels, and computerized tomography. Twenty-two patients – ten as second-line, 11 as third-line, and one as fourth line – received gemcitabine. Seven patients received six courses, nine cases three, five cases two and one case one course of treatment. There were four (18.2%) partial and two (9.1%) complete responses with an overall response rate of 27.3%. Stable disease was also observed in three more cases. The progression-free interval was found to be a median of three months. Grade 3-4 neutropenia was seen in two (9.1%) and grade 3-4 thrombocytopenia was seen in four (18.2%) cases. Pancytopenia was observed in one (4.5%) patient. There was no grade 3-4 non-hematological toxicity.

Antitumoral activity is encouraging in heavily pretreated ovarian cancer patients. A short progression-free interval is noticeable in responding cases. Toxicity is mainly hematologic and moderate.

Key words: Gemcitabine; Ovarian cancer; Chemotherapy; Toxicity.

Introduction

Gemcitabine hydrochloride, an antimetabolite, is a pyrimidine nucleoside analog. Gemcitabine exerts its chemotherapeutic action by inhibiting DNA replication and synthesis and by blocking repair mechanisms. Gemcitabine has been reported to have clinical activity on various solid tumors with tolerable toxicity. Clinical antitumor activity has been noted among pancreatic, lung, breast, bladder and ovarian cancers [1, 2].

We evaluated the response rates and toxicity profiles of gemcitabine in ovarian cancer patients in whom standard treatment fails.

Materials and Methods

Gemcitabine was used as a single-agent treatment in advanced epithelial ovarian cancer patients with recurrence or progression after standard treatment. All patients were operated on at four different departments by an experienced gynecologic oncologist. All patients except one had optimal debulking surgery (maximal residual tumor diameter less than 1.5 cm) including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy. Bowel surgery or retroperitoneal lymph-node debulking were added when indicated. All patients received platinum drugs (cisplatin or carboplatin) and paclitaxel as first-line chemotherapy. Gemcitabine was started in patients with recurrence earlier than two years after the first treatment or when tumor progression was observed after the second-line treatment.

Patients received gemcitabine, 1000 mg/m^2, by intravenous infusion over 30 minutes at 1, 8, 15 days of every 28 days. Every 28 day-cycle was accepted as one course. Serum CA 125 levels were repeated every 28 days. Measurable disease was followed with physical examination and computed tomography. Patients were considered to be in complete response if all signs and symptoms of the disease were lost after at least one-month duration. Patients were accepted as partial response if tumor regressed to more than half of the pretreatment size or lowering of serum CA 125 to half of the pretreatment levels. Patients were accepted as having stable disease if there was some response without meeting the above criteria.

Hematologic and non-hematologic toxicities were recorded through the treatment courses. Appropriate supportive treatments like blood or platelet transfusions were given when indicated. Granulocyte colony stimulating factor was added between treatment cycles when significant neutropenia was observed.

Results

The median age of the patients was 56 (20-70). Median pretreatment CA 125 level was 841 (10-6672). Histopathological types of the patients receiving gemcitabine are illustrated in Table 1. Twenty-two women – ten as second-line, 11 as third-line, and one as fourth line – received gemcitabine treatment (Table 2). Seven patients received six courses, nine cases three, five cases two and one case one course of treatment. There were four (18.2%) partial and two (9.1%) complete responses with an overall response rate of 27.3%. Stable disease was also observed in three more cases. The progression-free interval in patients with demonstrable response was found to be a median of three months.

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Table 1. — *Histopathological types of patients who received gemcitabine.*

Histological type	N	%
Serous	16	72.7
Endometrioid	4	18.3
Indifferentiated	1	4.5
Mixed (clear cell + endometrioid)	1	4.5
Total	22	100

Table 2. — *Previous amount of treatment regimens before gemcitabine*

Histological type	N	%
Treatment	1 regimen	10 patients
	2 regimens	11 patients
	4 regimens	1 patient
Total		22 patients

Toxicity was mainly hematological. Grade 3-4 neutropenia was seen in two (9.1%) and grade 3-4 thrombocytopenia was seen in four (18.2%) cases. Pancytopenia was observed in an additional one (4.5%) patient. There was no grade 3-4 non-hematological toxicity. Mild nausea and vomiting, fatigue, myalgias and hair loss were also seen.

Discussion

It has been reported in several studies that gemcitabine has some activity in heavily pretreated ovarian cancer patients [3-7]. These patients received either cisplatin or cisplatin with paclitaxel as first-line treatment. Single-agent gemcitabine was used in these patients when resistance to first-line treatment was seen or tumor progression was detected. Response rates were reported to be between 11-22% in these poor prognostic patients. Moreover, progression-free intervals were reported to be short, mostly a few months. The results of our study are compatible with the results of all the previous reports, with even better response rates. Higher response rates may be expected in untreated patients.

Gemcitabine doses in previous studies ranged between 800 mg/m^2 and 1250 mg/m^2. The best observed response rate was reported in patients who received 1250 mg/m^2 [6]. Even in these higher doses, toxicity was reported as acceptable and mainly hematological. All the patients who were treated with gemcitabine had exposure to more than one previous treatment regimen and the probability of cumulative toxicity should be kept in mind. Gemcitabine may have a more favorable toxicity profile in untreated women.

Because of the activity demonstrated by gemcitabine, its nonoverlapping toxicity profile with cisplatin and possible synergistic effect, combination treatments with cisplatin and gemcitabine should be evaluated in further studies.

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