Second-line with paclitaxel and carboplatin for recurrent disease following first paclitaxel and platinum compounds in ovarian carcinoma

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Summary

Objective: The combination of paclitaxel and platinum compounds is considered the best first-line regimen for advanced ovarian carcinoma. The purpose of this study was to evaluate a paclitaxel and carboplatin combination in pretreated patients who recurred within 24 months after a complete clinical response with the same regimen used as first-line chemotherapy.

Methods: 18 patients were included in this study. Second-line chemotherapy consisted of paclitaxel, 175 mg/m^2 as a 3-hour infusion, and carboplatin AUC 6 every 21 days.

Results: Among 15 evaluable patients, eight (53%) complete and five (34%) partial responses were observed, while two (13%) patients had stable disease (SD). The response rate was 67% among patients with measurable disease and 52% for evaluable disease. The median progression-free interval after second-line chemotherapy was 8.3 months. The median progression-free interval for patients with measurable disease was 8.6 months and for evaluable disease it was 7.9 months. Seven (46%) of 15 patients have developed recurrence after second-line chemotherapy with paclitaxel and carboplatin with a median time to recurrence of 9.8 months.

Conclusion: Paclitaxel 175 mg/m^2 and carboplatin AUC 6 as second-line chemotherapy in this sensitive population is effective in terms of response rate and progression-free interval.

Key words: Ovarian cancer; Paclitaxel; Carboplatin; Chemotherapy.

Introduction

Ovarian carcinoma is the most frequent cause of death among gynecologic malignancies [1]. Standard therapy for patients with ovarian carcinoma is based on primary cytoreductive surgery, followed by paclitaxel and platinum-based polychemotherapy and eventually second-look. Despite the high objective response rate the majority of patients with advanced disease will recur.

Patients with malignancies who relapse after first-line chemotherapy may respond again to the same (or similar) drugs [2-5]. However, there is not enough available information about the number of times this process can be repeated. Is it possible for a patient with ovarian carcinoma to respond to a paclitaxel and platinum regimen at the time of a second or third relapse?

The proposal of our study was to evaluate paclitaxel and platinum as second-line in patients treated with the same drugs.

Patients and Methods

Paclitaxel (Taxol) was administered intravenously at a dose of 175 mg/m^2 in 500 ml of normal saline solution as a 3-hour infusion on day 1, immediately followed by carboplatin at a fixed dose of AUC 6 in 500 ml normal saline, every 21 days for six courses. Treatment was delivered in an outpatient setting.

Antagonist 5-H T_3 receptors were used as an antiemetic regimen. Premedication with 125 mg prednisone orally, 12 and six hours before the paclitaxel infusion, 20 mg famotidine and 50 mg diphenhydramine given intravenously 30' before paclitaxel was recommended for all patients.

A total of 18 patients with ovarian carcinoma received the second-line combination paclitaxel plus carboplatin regimen described above.

Eligible patients were pretreated women with ovarian carcinoma (FIGO IIC-IIIA) who recurred within 24 months after a complete clinical response to paclitaxel and platinum compounds as first-line chemotherapy (Table 1). Before each treatment course patients had a complete history and physical examination, including bimanual pelvic exploration and neurologic assessment examinations. Further requirements were white blood count > 3500/μl, granulocyte count > 2000/μl, platelet count > 100,000/μl, bilirubin level < 1.4 mg/dl, and creatinine level < 2.0 mg/dl.

Colony-stimulating factors (GSFs) were employed for granulocyte counts < 2000/μl. After the first course weekly complete

Table 1. — *Patient characteristics*

No. of patients	18
Age (years)	
Median	58
Range	34-70
Histologic grade:	
Well differentiated	8
Moderately well differentiated	5
Undifferentiated	5
Total no. of courses	108
Valuated courses	90
No. of evaluable patients	3

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blood counts and serum chemistries were performed to evaluate hematologic toxicity; a baseline CT scan of the abdomen and pelvis was done after the third cycle of chemotherapy.

Response criteria

A complete response (CR) was defined as the complete disappearance of all evidence of disease for at least four weeks, confirmed by physical examination, CT scan and ultrasound.

Partial response (PR) was defined as a > 50% decrease in the sum of the products of the diameters of measurable lesions for at least four weeks.

Progressive disease (PD) was defined as an increase of > 25% in the size of the measurable lesions or the appearance of an inequivocal new lesion within two months of study entry.

Stable disease (SD) was defined as a steady state of response less than a PR or progression less than 25% of at least four weeks duration. The progression-free interval (PFI) was defined as the time from the first day of treatment until progression of disease.

Results

The median time to recurrence after-line therapy was ten months, with a range of 6-20 months. Fifteen of the 18 patients were evaluable. One patient who had received two courses was lost to therapy and in two cases of neurologic toxicity (grade 3) the treatment was stopped. Among 15 measurable and evaluable patients, eight (53%) demonstrated a complete response (CR), five (34%) demonstrated a partial response (PR) and two (13%) stable disease (SD). The response rate among patients included in the study with measurable disease was 67% and among the patients with evaluable disease it was 52%.

The median progression-free interval for all 15 patients after second-line chemotherapy with paclitaxel and carboplatin was 8.3 months (range 5-14 months). The median progression-free interval for patients with measurable disease was 8.6 months and for evaluable disease it was 7.9 months. Seven (46%) of 15 patients have developed recurrence after second-line therapy with paclitaxel and platinum with a median time to recurrence of 9.8 months.

No patients died before five months after the second-line therapy.

The toxicity of this regimen is expressed in Table 2. Twelve patients required colony-stimulating factors, with a total of 60 courses (66.7%).

Table 2. — *Toxicity*

General alopecia	15	(88.3%)
Severe emesis	5	(29.4%)
Mild emesis	10	(58.8%)
Severe myalgia	1	(5.6%)
Moderate myalgia	6	(35.2%)
Neurotoxicity grade 3	2	(11.7%)
Thrombocytopenia grade 3 or 4	14	(82.3%)
Sepsis	0	
Febrile neutropenia	0	

Discussion

Ovarian carcinoma is the leading cause of death among gynecologic malignancies.

Standard chemotherapy (as first-line after cytoreductive surgery) for patients with advanced ovarian cancer remains a combination of platinum and paclitaxel [4].

There is not complete agreement in the literature about the salvage chemotherapy regimen. However, polychemotherapy seems to be the most efficacious approach. Several investigators have reported a dose-response relationship suggesting that paclitaxel does not have a complete and maximal effect within the first cycles of therapy [5, 17]. Also several groups (GOG) have concluded that patients with ovarian cancer who initially respond to a platinum and paclitaxel-based regimen can respond a second time if the disease recurs [6, 7].

Second-line therapy with platinum (carboplatin) and paclitaxel in patients pretreated with the same regimen remains an interesting unanswered quistion [5]. Our experience seems to be consistent with the before-mentioned findings. The rationale for the combination of paclitaxel and platinum is in part based on the potential interactive mechanism of action of the two utilized drugs.

In addition to its ability to alter microtuble kinetics and stimulate apoptosis [8, 13, 14], paclitaxel has been shown to inhibit repair platinum-DNA adducts and also to synergize with X-irradiation. Platinum-DNA adducts and alkylation-DNA damage are repaired by different pathways, nucleotide excision repair for platin-DNA adducts and mismatch repair pathways for alkylation-DNA damage [15,16].

The encouraging clinical results observed with this regimen support the possibility that these multiple molecular interactions may occur concurrently.

Also in these cases it is less clear if these molecular interactions may occur in already treated cellular populations [17].

Moreover, the length of the progression-free interval is one of the main predictive factors of response to second-line treatments.

Some of our results confirm the efficiency of these pharmacodynamic interactions. Response rate of 13-53% have observed in patients with treatment-free intervals ranging from six to 18 months, while several reports have noted response rates of > 70% for individuals with a treatment-free interval of > 2 years [6].

The objective of this study was to evaluate paclitaxel and carboplatin (as second-line therapy) in pretreated patients with ovarian carcinoma who recurred within 24 months after a complete clinical response with a paclitaxel and platinum compound as first-line chemotherapy.

Recognizing the importance of the treatment-free interval in determining the change of a secondary response to platinum, the Gynecologic Oncology Group (GOG) has included this parameter in its definition of "platinum resistant ovarian cancer" utilized in experimental trials of new antineoplastic agents in this malig-

nancy [9]. Patients who recur within four months after the end of therapy are considered to be resistant to this class of cytotoxic agents. Many reports noted a secondary response to platinum in 30-75% of cases [2, 19]. Patients with ovarian carcinoma, already treated with paclitaxel, generally continue to maintain chemosensitivity beyond one or two recurrences [8, 11, 16].

Our study results show better values of response rate than other study reports.

Thigpen *et al.* observed a response rate of 43% in a Gynecology Oncology Group study involving 49 patients with ovarian cancer, 45 of whom were evaluable; the response rate was 40% [9].

Sarosy *et al.* [11] reported a response rate < 30%. Several factors may be responsible for these differences. One reason could be the different methods of using taxol (infusion and dose) by different groups of investigators. Heisenhauer *et al.* [10] observed a relationship between the dose of paclitaxel and its antitumor effects, but they did not observe a major role for infusion duration in antitumor efficacy. Furthermore, most patients received two or more prior chemotherapy regimens.

In our study all patients had only one prior chemotherapy. In contrast to other reports no grade 4 leukopenia or neutropenia was noted. This could be due to the application of colony-stimulating factors (GSFs) in 12 patients. In 14 patients (64 courses, 58.8%) we observed grade 3 or 4 thombocytopenia which was treated with 20 mg dexamethasone orally. The reported toxicity was similar to other studies [10].

Neurologic toxicity (sensory neuropathies and muscle weakness) was a clinically significant adverse effect in our study [11]. In these cases the cessation of paclitaxel was necessary.

Finally, our patients' responses seem to be greater than those published in other studies.

In view of the favorable response rate and toxicity profile our study strongly suggests resistant disease should be demonstrated in patients before using other chemotherapy regimens. This recommendation would need to be modified if future investigative efforts demonstrate that an alternative treatment strategy has potential results for more durable remissions.

Our study confirms the therapeutic benefit of paclitaxel and carboplatin in already treated patients with ovarian carcinoma who recurred within 24 months after a complete clinical response with paclitaxel and platinum compound as a first-line chemotherapy.

In view of our relatively small sample, a confirmation of our findings is warranted by assessing larger sample populations and using well-designed randomized trials.

In a chemotherapy-sensitive population the activity of alternative second-line regimens must be interpreted with this approach.

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