Preliminary experience with salvage weekly paclitaxel in women with advanced recurrent ovarian carcinoma

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Summary

Purpose of investigation: To assess the role of palliative chemotherapy with weekly paclitaxel in patients with recurrent ovarian cancer.

Methods: Thirty-two patients with paclitaxel- and platinum-resistant ovarian cancer were treated with weekly paclitaxel at 80 mg/m^2 as a 1-hour intravenous infusion weekly for six weeks every eight weeks (1 cycle). This schedule was considered to be given for three cycles. Evaluation of radiographically measurable disease was used in the assessment of response. CA-125 was used to classify responses only in the absence of a measurable lesion.

Results: Thirty-two patients were all assessable for response. Of these, nine patients (28.1%) achieved a partial response and one patient achieved a complete response, leading to an overall response rate of 31.2%. Stable disease occurred in six patients (18.8%), and 16 patients (50%) had progressive disease. Nine patients died of progressive disease while on treatment. The median survival for the entire group was 10.5 months (range 2.5-22 months). Grade 3 or 4 leukopenia and neutropenia occurred in eight and six patients, respectively. Four of these patients developed febrile neutropenia without infection. Grade 1 and 2 peripheral neuropathies were observed in 50% of the patients without causing any premature drop out. Severe (grade 3 or 4) peripheral neuropathy was not observed. There were 11 patients with grade 1 or 2 myalgias.

Conclusion: Weekly paclitaxel regimen is well tolerated with acceptable toxicity. The favorable toxicity profile and the encouraging antitumor activity observed in this study makes this regimen an option for the salvage treatment of patients with recurrent ovarian cancer.

Key words: Recurrent ovarian cancer; Paclitaxel; Weekly regimen; Salvage therapy.

Introduction

Ovarian cancer is the fifth leading cause of cancer death in women. Most patients with ovarian cancer respond to first-line chemotherapy, but many relapse within 18 to 22 months. Unfortunately, ovarian cancer is usually asymptomatic until the tumor has progressed to an advanced stage [1]. Approximately 70% of women with ovarian cancer initially present with Stage III or IV disease [2]. Currently, the standard of care for newly diagnosed advanced-stage ovarian cancer includes cytoreductive surgery followed by combination chemotherapy with platinum (either cisplatin or carboplatin) and paclitaxel. However, 50%-80% of the patients who respond to this combination regimen will eventually relapse [3]. Paclitaxel has been established as an important initial component of ovarian cancer chemotherapy, and should be considered in the management of patients with recurrence. In addition, the mechanisms of acquired drug resistance are different between paclitaxel and platinum, and not all patients with platinum-resistant disease are resistant to paclitaxel, even if paclitaxel was included in their front-line treatment program [4].

High doses of chemotherapeutic agents have conventionally been administered to patients with cancer, but such regimens require an extended treatment-free period to allow recovery of normal host cells, such as the hematopoietic progenitors. During this treatment-free period, however, cancer cells and vascular endothelial cells in the tumor tissue might also resume growth, possibly with higher drug resistance or biologic aggressiveness. Weekly administration of chemotherapy appears to be most effective with phase-specific, not rapidly cytotoxic drugs and those with a medium half-life, such as paclitaxel. The administration of weekly paclitaxel provides exposure of the tumor to the drug such that there is an increase not only in the intensity but also in the density of the dose [5].

Dose-dense paclitaxel may inhibit tumor regrowth between cycles and limit the emergence of malignant cell populations resistant to chemotherapy. As has been demonstrated in experimental systems, paclitaxel also has a capacity to promote apoptosis, albeit at doses lower than that necessary to produce a block in the mitosis process. As such, the agent possesses an antiangiogenic action. More frequent exposure to paclitaxel may also enhance its apoptotic and antiangiogenic effects [5-7]. The purpose of this study was to examine the efficacy and side-effect profile of a weekly schedule of paclitaxel for patients with platinum-paclitaxel refractory, recurrent ovarian cancer.

Material and Methods

Between February 2000 and December 2002, 32 patients with platinum-paclitaxel refractory ovarian carcinoma were enrolled in this trial. Patients were eligible if they had recurrent ovarian carcinoma that was histologically confirmed at primary diagnosis. All patients had either measurable or assessable

Revised manuscript accepted for publication June 15, 2004

disease. Disease was classified as measurable if the patient had bidimensionally measurable disease by computed tomography (CT). Assessable disease was only used in patients with no measurable disease and was defined as CA-125 ≥ 75 U/ml. Eligible subjects were required to have a life expectancy of more than three months with an Eastern Cooperative Oncology Group (ECOG) performance status less than 3. All patients had received prior platinum-based chemotherapy for advanced ovarian cancer. In addition, all patients had also received at least one regimen that contained paclitaxel.

Patients had to have adequate hematologic (granulocyte count of ≥ 1500/ml and platelets of ≥ 100,000/ml), hepatic (bilirubin and SGOT of < 2X institutional upper limit of normal), and renal functions (creatinine < 2 mg/dl); a life expectancy of > 3 months.

Pretreatment evaluation consisted of history and physical examination, electrocardiogram, and assessment of performance status. All patients had a chest X-ray and computed tomography scan of the abdomen and pelvis for disease assessment, including measurable disease assessment within 30 days prior to registration. Laboratory studies, including differential and complete blood cell count (CBC), serum chemistry and CA-125, were done within two weeks of registration. Toxicities, CBC, blood chemistry, and CA-125 were assessed before each course, and scans for tumor measurements were done every other month or earlier if clinically indicated. The standard WHO criteria were used for evaluation of toxicities.

Study design

This study was a noncomparative multicenter study of weekly paclitaxel. The investigative sites involved were Ankara University School of Medicine and the University of Uludag. All investigative sites obtained institutional review board approval and all patients provided signed informed consent.

Treatment

Paclitaxel (Taxol®, Bristol-Myers-Squibb, Princeton, NJ) was given at a dose of 80 mg/m^2 as a 1-hour intravenous infusion weekly for six weeks every eight weeks (1 cycle). This schedule was considered to be given for three cycles. Thirty minutes prior to each treatment, patients were medicated intravenously with 10 mg of dexamethasone, 50 mg of diphenhydramine, and 50 mg of ranitidine.

At the time of each scheduled treatment, paclitaxel was administered if the absolute white blood cell count (WBC) was ≥ 1,500/ml and the platelet count was ≥ 100,000/ml. If not, the treatment was delayed until recovery of hematologic toxicity. If there was no improvement in the findings, the therapy was discontinued.

Response assessment

Responses were classified based on the same methodology used to define disease status at enrollment. Patients with radiographically measurable disease underwent repeat radiologic studies every other month. CA-125 was used to classify responses only in the absence of a measurable lesion; CA-125 response criteria were based on established guidelines [8, 9]. A complete response was defined as complete disappearance of all measurable and assessable disease for four weeks or, in the absence of measurable lesions, normalization of the CA-125 level for at least four weeks. A partial response was a 50% or greater reduction in the product obtained from measurement of each bidimensional lesion for at least four weeks or a drop in the CA-125 by at least 50% for at least four weeks. Disease progression was defined as a 50% or greater increase in the product from any lesion documented within eight weeks of study entry, the appearance of any new lesion within eight weeks of entry into the study, or any increase in the CA-125 from baseline at study entry. Stable disease was defined as disease not meeting any of the above criteria.

Patients were to continue on protocol until disease progression or adverse effects necessitated removal from the study. Patients could also be removed from the protocol at the discretion of the treating physician. Withdrawal from the study at patient request was allowed at any time. When a complete response was documented, patients were treated with six more courses (1 cycle) of weekly paclitaxel prior to discontinuation of treatment.

Results

Table 1 illustrates the patients' characteristics. Thirty-two patients with platinum-paclitaxel refractory, recurrent ovarian cancer were enrolled with a mean age of 55.4 years (range 24-75). No patients refused chemotherapy after registration. The mean number of prior salvage chemotherapy regimens was two (range, 1-5). Thirty-two patients received a total of 326 one-week treatment courses with paclitaxel, for an average of ten weeks of treatment per patient. Twenty-eight of 32 patients (87.5%) completed a minimum of one cycle (6 weekly courses). Eight patients suffered treatment delays secondary to low WBC counts. All patients were evaluated for toxicity and response.

Table 1. — *Patient characteristics (n = 32).*

Mean age, in years (range)	55.4 (24-75)
ECOG performance score (number of patients)	
0	5
1	18
2	9
Number of patients with measurable disease	20
Number of patients with assessable disease	12
Histology	
Papillary-serous	24
Endometrioid	4
Mucinous	3
Clear cell	1
Number of prior chemotherapy regimens	
Mean	2
Range	1-5
Presence of ascites	9
Drug-free intervals, in months	
Mean	5.5
Range	2-18

Toxicities of Therapy

All patients were assessable for documentation of toxicity. Despite extensive prior therapy, toxicity generally was mild and did not necessitate dose reduction. There were no episodes of sepsis or chemotherapy-related fatality.

Major hematological and nonhematological toxicities are listed in Table 2. Myelotoxicity, specifically neutropenia, was the major toxicity commonly encountered in this study. Grade 3 or 4 leukopenia and neutropenia occurred in eight and six patients, respectively. Four of these patients developed febrile neutropenia without infection. Although febrile episodes were of brief duration (≤ 3 days), patients were hospitalized for adequate

Table 2. — *Hematological and nonhematological toxic effects of 1-hour weekly paclitaxel therapy.*

Toxic effect	WHO Grade			
	1	2	3	4
Leukopenia (n)	5	2	5	3
Neutropenia (n)	2	3	2	4
Thrombocytopenia (n)	6	2	0	0
Anemia (n)	9	5	3	4
Peripheral neuropathy (n)	14	2	0	0
Myalgias (n)	7	4	0	0
Alopecia (n)	0	6	0	0

n = Number of patients expressing relevant treatment-related toxic effects.

treatment with intravenous antibiotics. Granulocyte colony-stimulating factor (G-CSF) support was used for three patients with grade 3 or 4 neutropenia since neutropenia did not recover before the next cycle. Thrombocytopenia was observed in eight patients, but was not severe. Fifteen blood transfusions were required to elevate hemoglobin concentrations above 9 g/dl in seven patients. Hematological side-effects were generally not associated with severe complications. Cumulative hematological toxicity was not observed.

As expected, neurotoxicity was the most frequently observed nonhematological toxicity. Fortunately, this was mainly represented by grade 1 peripheral neuropathy, predominantly of sensory type and nondisabling, limited to finger and/or toe tips (44% of the patients). Grade 2 neuropathy was observed in 6% of the patients without causing any premature drop out. Severe (grade 3 or 4) peripheral neuropathy was not observed. There were 11 patients with grade 1 or 2 myalgias. Alopecia was of moderate intensity and use of a weekly 1-hour infusion schedule resulted in alopecia in only six of 32 patients. Nausea/emesis, diarrhea and mucositis were uncommon and none of the patients needed antiemetic support. In general, the 1-hour infusion was well tolerated, with no episodes of anaphylaxis or hypersensitivity. The most relevant treatment-related nonhematological toxicities are summarized in Table 2.

Response to therapy

Thirty-two patients were all assessable for response. Of these, nine patients (28.1%) achieved a partial response and one patient achieved a complete response, leading to an overall response rate of 31.2%. Stable disease occurred in six patients (18.8%), and 16 patients (50%) had progressive disease. Nine patients died of progressive disease while on treatment. The median survival for the entire group was 10.5 months (range 2.5-22 months).

Discussion

Despite high overall clinical response rates achieved with combination platinum-taxane therapy (up to 80%), including a high proportion of complete responses, most patients with ovarian cancer subsequently relapse and develop drug-resistant disease. Thus, the primary goal of therapy in relapsed ovarian cancer is to extend survival and preserve quality of life. Therapeutic options include retreatment with platinum and/or paclitaxel, although patients retreated with carboplatin and paclitaxel are at increased risk from cumulative hematologic toxicity [2, 10, 11]. Other treatment options in the relapsed setting include initiation of a non-cross-resistant chemotherapy agent or the use of investigational agents in the context of a clinical trial. The optimal management of patients with recurrent ovarian cancer has not yet been established. Most patients with ovarian cancer who have undergone heavy pretreatment with platium- and/or paclitaxel-based chemotherapies scarcely respond to second-line drugs and the rates of cure are very low. Thus, the treatment of recurrent ovarian cancer still constitutes a challenge for the clinician. Weekly administration of paclitaxel by 1-hour infusion has been reported to have less toxicity and a promising effect in these cases. Previous reports have demonstrated that weekly paclitaxel administration in a 1-hour infusion at doses of 60-100 mg/m^2 is an acceptable salvage regimen [12-14].

Several studies have looked at treatment with weekly paclitaxel by 1-hour infusion in patients with recurrent ovarian cancer. In 13 assessable patients, four partial responses were observed (30%) in a study performed by Fenelly *et al.* [15]. Additionally, two patients with disease progression receiving standard 3-week paclitaxel schedules demonstrated a response with weekly paclitaxel treatment. Abu-Rustum *et al.* retrospectively reviewed the medical records of 45 patients with advanced, recurrent epithelial ovarian cancer treated with single-agent weekly intravenous paclitaxel (60 to 100 mg/m^2, 1-hour infusions) [16]. Patients received a median of nine cycles of weekly paclitaxel (range, three to 37), with a median interval of eight months (range, 1 to 32 months) between the last paclitaxel treatment and the institution of weekly therapy. Response was noted in 13 of 45 (28.9%) patients. Similar to other studies, it was demonstrated that chemotherapy was generally well tolerated, with treatments completed on a weekly schedule and only one hospitalization for nadir fever. They concluded that weekly intravenous paclitaxel was an active and well tolerated regimen in heavily pretreated women with recurrent ovarian carcinoma. The highest response rates with weekly paclitaxel regimen were reported by Kaern *et al.* [17]. In that study 31 patients, 80% of whom had Stage III–IV disease with recurrent ovarian cancer resistant to platinum, were treated with weekly paclitaxel 80 mg/m^2/week in a 1-hour infusion. Patients received a median of 14 (range 7-22) courses and an overall response rate of 55% (2 complete responses, 15 partial responses) was achieved. No complete responses were seen in patients with multiple resistant (paclitaxel and platinum) disease, but nine (45%) of these patients had partial responses and four (20%) had stable disease. Median survival was nine months and median progression-free survival was 4.9 months. No treatment was stopped due to toxicity. In our study, most of the findings were relevant to the current literature. Nine out of 32 patients (28.1%) achieved a partial response and one patient achieved a complete response, leading to an overall response rate of 31.2%. Stable disease occurred in six patients (18.8%), and 16 patients (50%) had progres-

sive disease. The median survival for the entire group was 10.5 months (range 2.5-22 months). These findings were considered as favorable in this group of patients.

A phase I pharmacologic study of weekly paclitaxel in patients with relapsed ovarian cancer reported dose-intense paclitaxel delivery with a favorable toxicity profile [15]. They found dose-limiting toxicity at a paclitaxel dose of 100 mg/m²/week in a group of heavily pretreated patients. Escalating doses of paclitaxel 40, 50, 60, 80 and 100 mg/m²/week were administered to patients with recurrent ovarian cancer who had all received prior paclitaxel and cisplatin therapy. The authors concluded that weekly paclitaxel was well tolerated, did not result in cumulative myelosuppression and had a favorable toxicity profile. In a retrospective review of 22 women with recurrent epithelial ovarian carcinoma, the median dose of paclitaxel was 80 mg/m² (range, 60-80 mg/m²) [18]. During a total of 325 weeks of paclitaxel treatment, only 13 treatment delays occurred (hematologic indication, 9; nonhematologic indication, 4). No cases of grade 4 hematologic toxicity, sepsis, or worsening neuropathy were documented. Likewise, in our study, hematological side-effects were generally not associated with severe complications, despite the fact that myelotoxicity, specifically neutropenia, was the major toxicity commonly encountered. Additionally, cumulative hematological toxicity was not observed. Grade 3 or higher neutropenia was observed in 18.7% of patients and three patients required G-CSF support.

As expected, neurotoxicity was the most frequently observed nonhematological toxicity. In the present study, neurotoxicity was usually mild to moderate; no grade 3 or 4 severities were encountered. In a randomized trial of paclitaxel monotherapy, a prevalence of 29% for grade 2 and 3 neuropathy was noted in the conventional arm comparing with 11% in the weekly arm [19]. Two publications suggest that the threshold concentration to induce neuropathy is 100 mg/m² of paclitaxel weekly [20, 21]. When paclitaxel is given on a weekly basis, various premedication regimens have been used [22, 23]. In the current study, patients were given dexamethasone 10 mg IV. Neither mild nor severe hypersensitivity reactions occurred and no major corticosteroid side-effects were observed. Thus, we propose this premedication regimen to avoid problems with the corticosteroid intake in case of treatment with paclitaxel 80 mg/m²/week by 1-hour infusion.

In conclusion, we believe that weekly application of paclitaxel allows delivery of a higher dose in a shorter time. The favorable toxicity profile and the encouraging antitumor activity observed in this study makes this regimen an option for the salvage treatment of patients with recurrent ovarian cancer.

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