ORIGINAL ARTICLES

A phase II study of weekly paclitaxel in platinum and paclitaxel-resistant ovarian cancer patients

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Summary

Objective: In platinum-resistant ovarian cancer weekly paclitaxel has shown an equal efficiency and better toxicity profile compared to three-weekly paclitaxel in platinum-resistant ovarian cancer. We wanted to study response rate, response duration and toxicity in platinum-resistant tumors with emphasis on tumors also resistant to three-weekly paclitaxel.

Material and Methods: Fifty-seven patients with platinum-resistant disease, treated with weekly paclitaxel 80 mg/m^2, 1-hour infusion, were evaluable for response and toxicity (Group A). Of these, 39 patients (Group B) had tumors resistant to paclitaxel as well.

Results: Overall response rate was 56% (12% CR, 44% PR, 19% SD, 25% PD) and 49% in group B: 5% CR, 44% PR, 23% SD, 28% PD. Median progression-free survival was 5.0 months and 4.0 months in group A and B, respectively. Median survival was 13.7 months in both groups. Toxicity was mild. Only two patients had grade 2 neutropenia and no neutropenic fever was recorded. No worsening in pre-existing neurotoxicity or hypersensitivity reactions was observed.

Conclusion: Weekly administration of paclitaxel is associated with promising response rates in patients with platinum- and paclitaxel-resistant ovarian cancer. The treatment is well tolerated with non-cumulative hematologic and non-hematologic toxicity.

Key words: Weekly paclitaxel; Platinum- and Paclitaxel-resistant ovarian cancer.

Introduction

Ovarian cancer is the sixth most common malignancy in women worldwide and has the highest mortality rate, responsible for about 106,000 deaths annually [1]. One reason for this is the lack of symptoms in early stages and at the time of diagnosis the majority of patients will have spread of disease beyond the ovaries, with 25%, 11%, 47% and 17% of the cases in FIGO stage I, II, III and IV, respectively. Survival figures have improved during the past two to three decades [2-5] but long-term survival or cure rates are still disappointingly low. This slight improvement in overall survival for patients with advanced disease might be explained by more extensive debulking surgery and modern chemotherapy.

Introduction of platinum in first-line combination chemotherapy has produced the highest response and progression-free survival rates [6, 7]. A benefit of anthracyclines has been suggested in several meta-analyses [8]. A significant improvement in response rate, PFS and overall survival introducing paclitaxel in frontline therapy was shown by Mc Guire in a randomized trial (GOG 111) finding the new combination of cisplatin and paclitaxel superior to the standard therapy cisplatin and cyclophosphamide [9].

In spite of the fact that up to 80% of advanced ovarian cancer patients respond to initial modern combination chemotherapy, the majority will recur and die of disease resistant to available cytotoxic agents. For patients with platinum-resistant disease there has, until now, not been any improvement in survival. In this group of patients drugs like hexamethylmelamine, iphosphamide and doxorubicin have shown response rates of less than 20% [10-12]. The antimitotic agent, paclitaxel, which acts by stabilizing and promoting microtubuli assembly has demonstrated significant activity in platinum-resistant disease. McGuire *et al.* reported a 25% response rate in patients with persistent/resistant epithelial ovarian cancer [13].

Since that time several phase II studies of paclitaxel monotherapy in recurrent and resistant disease have demonstrated response rates between 20-48% with durable responses in some patients [14, 15].

In the majority of ovarian cancer trials studying the efficacy of paclitaxel, the agent has been given in a three-weekly schedule with different infusion times. Early clinical trials in recurrent ovarian cancer showed equal efficacy of weekly paclitaxel with a better toxicity profile with less neuro- and myelotoxicity as compared to a three-weekly schedule [16, 17]. Anderson *et al.* demonstrated a 42% response rate in platinum-sensitive tumors and 22% in platinum-resistant tumors with the weekly schedule [18].

The possible efficacy benefit of a dose-dense weekly schedule with less toxicity made us design a protocol in a phase II setting with the aim of studying toxicity, feasibility, response rate, and duration of response as primary end-points. Secondary end-points were progression-free survival and survival in platinum resistant disease with special emphasis on platinum- and paclitaxel- (three-weekly schedule) resistant disease.

Materials and methods

From September 1998 to January 2001 a total number of 66 patients with histologically or cytologically confirmed recurrent epithelial ovarian cancer were treated with weekly paclitaxel (w-tax). Of these, 57 were considered eligible as they had platinum-

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resistant disease and were evaluable for response and toxicity (Group A). Within this group 39 patients had tumors that also were resistant to a three-weekly paclitaxel schedule (Group B).

Platinum resistance was defined according to the criteria of Markman [19] as relapse within a platinum-free interval of less than six months. Platinum refractory disease was defined as direct progression on platinum-based therapy and/or relapse within three to four months from the end of this treatment. The same criteria were used for paclitaxel resistant/refractory disease after paclitaxel based treatment. The recurrent lesion had to be measurable either clinically (palpable lesion > 2 cm) and/or by radiologic examination (MRI or CT scan with one diameter of at least 0.5 cm). Normal bone marrow function (neutrophils > 0.5 x 10^9/l , platelets > 100 x 10^9/l), kidney function (creatinine < 1.5 x upper normal level and liver function (bilirubin > 1.5 times and/or ALAT > 3 times upper normal level) was required. No cytotoxic chemotherapy was allowed four weeks before start of w-tax. Patients had to have an ECOG performance status of ≥ 1 and an expected lifetime of at least three months. Previous allergic reaction to paclitaxel treatment, symptoms of ongoing infection and pre-existing neurologic toxicity of grade 2 or more, were exclusion criteria. Response was assessed according to standard WHO [20] and CA 125 criteria [21-22].

Treatment schedule

Paclitaxel (Taxol®) was given intravenously 80 mg/m² as a 1-hour infusion in 250 ml NaCl 0.9% 30 minutes after premedication with Dexametason 4 mg IV, Dexchlorpheniramin 5 mg IV and Cimetidin 300 mg IV. Through the last year premedication was omitted after the first two courses. The first course was always given at our department. The following seven courses were given in an outpatient setting at local hospitals throughout Norway. The first response and toxicity evaluation was done one week after the eighth course. Patients with progression went off study. Responding patients and patients with stable disease continued treatment until progression or unacceptable toxicity. Response and toxicity evaluation was done after the 16th course and then after every fourth course.

Dose modification

In case of a neutrophil count < 0.5 x 10^9/l, the course was delayed until elevation of neutrophils > 0.5 x 10^9/l, and the w-tax dose was reduced one dose level to 70 mg/m². No dose escalation was allowed. If the neutrophil count had not recovered after two dose reductions (second dose level was 60 mg/m²) the patients went off the study.

Statistical analysis

The duration of response was calculated from the date of maximum response to date of progression or sensored date (01/06/01). Progression-free survival (PFS) was calculated from the date of the first w-tax course to date of progression or sensored date. Survival (OS) was calculated from the date of the first w-tax course to date of death or sensored date. Survival distribution was estimated by the Kaplan and Meyer method [23]. Toxicity was graded according to the WHO criteria [24]. All analyzed data were validated through the process of active monitoring throughout the study period.

Results

Patients characteristics

The characteristics of the 57 patients (Group A) with platinum-resistant disease are listed in Table 1 together with the subgroup consisting of 39 patients (Group B) with tumors also resistant to three-weekly paclitaxel. The median age of the patients at time of treatment with w-tax was 56 years, range 33-75. In all but four patients the recurrent lesion was more than 2 cm and more than one measurable lesion was present in 84%. The number of treatment lines before w-tax is listed in Table 2. All

Table 1. — *Patient characteritics.*

	Group A	Group B
Number of patients	57	39
FIGO stage		
I	7	6
II	2	1
III	38	25
IV	10	7
Histologic type		
serous	46	29
endometroid	2	1
clear cell	4	4
adenocarcinoma nc	5	5
Grade of differentiation		
highly	4	3
moderate	10	7
poorly	39	25
not graded	4	4
Size of largest lesion		
< 2 cm	4	4
2 to 5 cm	24	15
> 5 cm	29	20
Number of lesions		
single	9	7
two	17	9
three	14	10
multiple	17	13
Localization of recurrence		
pelvic	7	6
abdomen	37	24
abdomen+distant	11	7
distant	2	2

Table 2. — *Prior chemotherapy and number of treatment lines.*

	Group A	Group B
First-line	57	39
platinum	14	10
platinum+paclitaxel	28	18
paclitaxel+epirubicin+carboplatin	8	7
cisplatinum+doxorubicin	7	4
Number of platinum lines		
1	24	21
2	23	12
3	10	6
Number of platinum+paclitaxel lines		
none	12	8
1	37	25
2	8	6
Number of treament lines before w-tax		
1	11	11
2	17	9
≥ 3	29	19
Platinum refractory disease	15	10
Platinum+paclitaxel refractory disease	8	8

patients had platinum-based primary chemotherapy. However, two stage I patients had been treated with adjuvant intraperitoneal isotopes and received platinum at the first relapse. Only three patients were paclitaxel naive when treated with w-tax. All the 54 patients previously receiving paclitaxel had been treated with paclitaxel 175 mg/m^2, 3-hour infusion, as a single agent or in combination with platinum. W-tax was given as second-line therapy in 19% of the patients. Of the patients with disease also resistant to paclitaxel (Group B), 28% received w-tax as second-line therapy. Half of the patients had received three or more treatment lines before w-tax (Table 2). The medium treatment-free interval (TFI) was one month, range 1 to 41. Only five patients had TFI more than six months. The median platinum-free interval was six months, range 1 to 159. Of these patients 25 had received platinum based therapy within six months. The median paclitaxel-free interval for the 54 patients previously treated with paclitaxel was 11 months, range 1 to 74. In Group B the median time from earlier paclitaxel therapy to w-tax was 6.5 months, range 1 to 74. Fifteen (25%) of the patients had platinum refractory disease and eight of these also had paclitaxel refractory disease. For these patients with platinum refractory disease the median time from recent platinum treatment was 2.7 months (range 1 to 17) and the median TFI was one month (range 1 to 3 months). For the eight patients with platinum and paclitaxel refractory disease the median time from recent paclitaxel therapy was 2.7 months, (range 1 to 11) and median TFI was one month (range 1 to 3 months).

A total of 23 patients had been treated with anthracyclines before w-tax, 15 were treated in first-line and eight for recurrent disease. The first-line treatment in these patients consisted of TEC (paclitaxel + epirubicin +carboplatin) in eight patients and of cisplatin + doxorubicin in seven patients (Table 2). Within subgroup B altogether 19 patients had received anthracyclines, 11 in first-line (Table 2) and eight due to relapse.

Treatment and efficacy

A total of 806 courses of w-tax were given to the 57 patients. All received at least seven courses. The median number of courses was 14 (range 7 to 27). The corresponding figures in subgroup B was a median 13 courses (range 7 to 27). Responding patients (7 complete response, CR and 25 partial response, PR) received a median of 18 courses (range 9 to 27). Seven (12%) patients obtained complete remission, 25 (44%) partial remission and 11 (19%) had stable disease while 14 (25%) progressed on w-tax (Table 3). PR was obtained in 24 patients after eight courses and in one patient after 16 courses. Two of the CR patients had PR after eight courses and CR after 16 courses. The other five CR patients had responded by the eighth course. The response and survival data are shown in Table 3. The overall response rate was 56%. None of the 15 patients with platinum refractory disease obtained CR but nine (60%) of these had PR. The corresponding figures in the subgroup of patients with platinum- and paclitaxel-resistant disease are shown in Table 4. The total response rate in this group was 49% (5% CR and 44% PR). Twenty-three percent of patients had stable disease and 28% progressed. Of the eight with platinum- and paclitaxel-refractory disease three (38%) had PR while half of the patients progressed.

Table 3. — *Response, response duration, progression-free survival (PFS) and survival in platinum-resistant tumors; Group A, no. = 57.*

Response	No. of patients	Median duration, range, in months	Median PFS, range, in months	Median survival, range, in months
CR	7	6.5, 4.5 - 15.5	8.3, 6.0 - 19.4	10.2, 8.2 - 20.7
PR	25	3.0, 1.0 - 14.0	5.4, 3.8 - 16.4	12.5, 5.7 - 22.5
SD	11	3.0, 2.0 - 9.5	3.1, 1.8 - 9.7	11.0, 5.9 - 19.7
PD	14	-	2.0, 1.4 - 2.7	6.5, 3.2 - 24.6

• 3 CR patients (6.5+, 7.0+,14.0+) and 1 PR patient (14.0+) are still in remission.

Table 4. — *Response, duration of response, progression-free survival (PFS) and survival in platinum- and paclitaxel-resistent disease; Group B, n° = 39.*

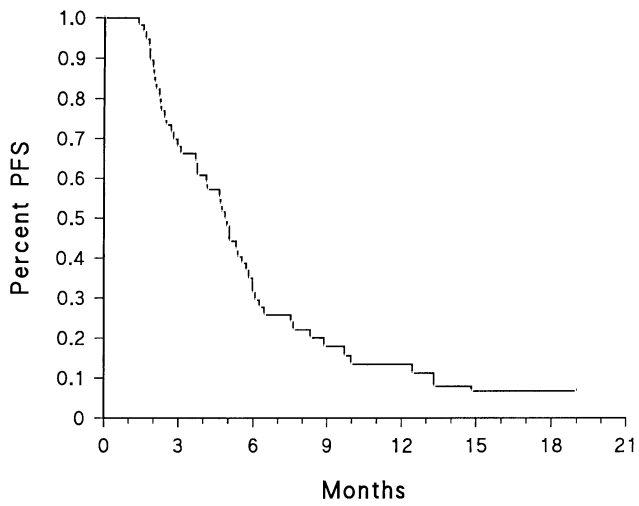
Response	No. of patients	Median duration, range, in months	Median PFS, range, in months	Median survival, range, in months
CR	2	9.3, 4.5 - 14.0	13.0, 10.0 - 15.9	3.0, 10.2 - 15.9
PR	17	3.0, 1.0 - 14.0	5.5, 3.8 - 16.4	13.7, 7.1 - 22.5
SD	9	3.0, 2.0 - 9.5	3.1, 2.2 - 9.7	13.8, 7.9 - 9.7
PD	11	-	2.0, 1.6 - 2.7	6.4, 3.2 - 9.5

No correlation was found between response to w-tax and FIGO stage, histologic type, grade, age, size and/or number of recurrent lesions, nor to previous treatment or number of treatment lines.

Of 23 patients previously receiving anthracyclin treatment ten (43%) responded to w-tax (1CR and 9 PR) compared to 22 (65%) of 34 patients not previously receiving anthracyclin therapy (6 CR and 16 PR). One of two patients with stable disease receiving anthracyclines responded with CR to w-tax. Within group B the corresponding figures were: 19 of the 39 had previously been treated with anthracyclins and nine (47%) of these responded to w-tax compared to ten of the 20 patients not previously receiving anthracyclins.

The CA125 level was not informative for response evaluation in five patients (1 CR, 1 PR, 1 stable disease, SD and two progressive disease, PD) as the level was less than 35 kU/l at relapse. Of eight CR patients with informative CA125, the clinical response was confirmed by the CA125 criteria. This was also the case for the ten patients considered to have clinically stable disease, although in one of these patients with clinical SD for five months CA125 normalised during treatment (from 75 kU/l to 6-4-14 with 1-month intervals). For the 24 CA125 evaluable PR patients, three cases were not confirmed by CA125. In one of the cases CA125 was unfortunately not taken monthly at follow-up and in another case CA125 was not taken before the date of progression three months later. In the third patient clinical PR could not be confirmed by CA125 (10810 kU/l -242-2710-29840). In this case the clinical duration of response was only two months confirming CA125 as an important marker of progression.

1a



1b

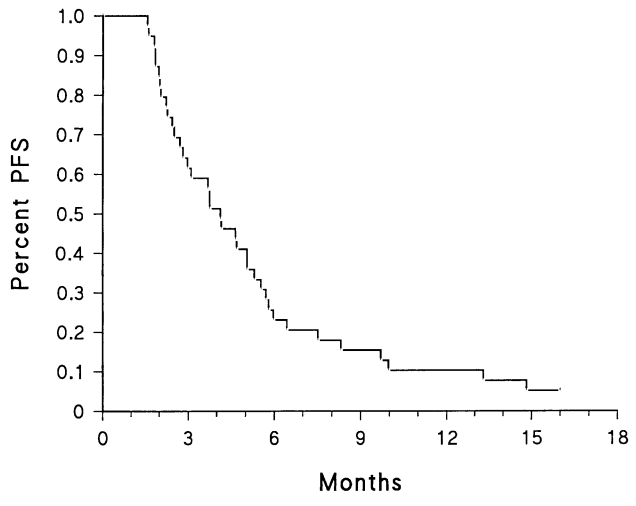
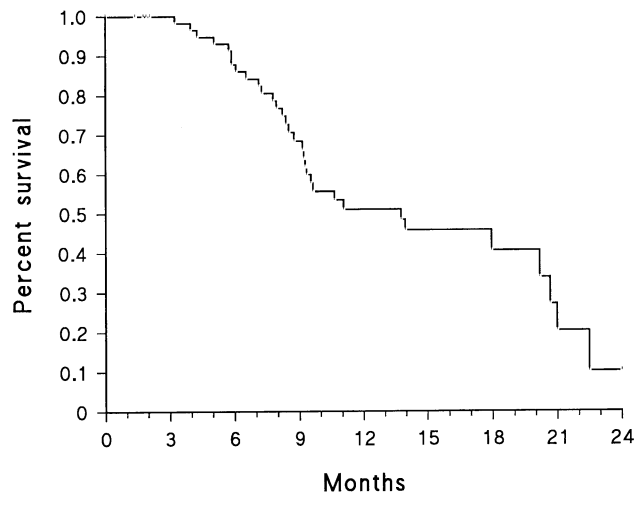


Figure 1a. — Progression-free survival probability in 57 ovarian cancer patients with platinum-resistant tumors treated with weekly paclitaxel.
Figure 1b. — Progression-free survival probability in 39 ovarian cancer patients with platinum- and paclitaxel-resistant tumors treated with weekly paclitaxel.

2a



2b

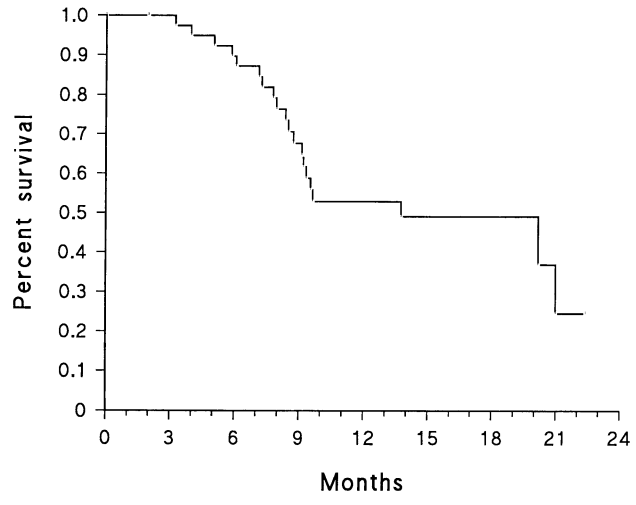


Figure 2a. — Survival probability in 57 ovarian cancer patients with platinum-resistant tumors treated with weekly paclitaxel.
Figure 2b. — Survival probability in 39 ovarian cancer patients with platinum- and paclitaxel-resistant tumors treated with weekly paclitaxel.

The median progression-free survival in Groups A and B was 5.0 months (range 1.5 to 19.5) and 4.0 months (range 1.6 to 16.4), respectively (Figures 1a and b). The median survival was 13.7 months (range 3.2 to 24.5) and 13,7 months (range 3.2 to 22.5) in Groups A and B, respectively. Three of the CR patients and one of the PR patient are still in remission. Another PR patient stopped treatment due to toxicity. In total 21 patients are still alive.

Toxicity

In general toxicity was mild and only one patient stopped treatment due to toxicity (grade 3 neurotoxicity). Toxicity is listed in Table 5. Bone marrow loss was a main concern, but only two patients showed grade 2 neutropenia and no neutropenic fever was observed. The known paclitaxel adverse effects such as arthralgia and myalgia were less common and severe following the three-weekly schedule. Alopecia was mild but difficult to evaluate as many of our patients had alopecia before starting w-tax treatment due to recent chemotherapy. Alopecia became more frequent with increasing treatment time. The same was the case for nail changes which only became a problem if treatment continued for more than 16 courses. The majority of our patients had mild pre-existing neurotoxicity after previous chemotherapy, but we did not observe any worsening during w-tax treatment except for one patient with grade 2-3 neurotoxicity at inclusion who stopped treatment due to increasing symptoms. We did not observe any hypersensitivity reaction although premedication was stopped after the second course. Fatigue was not a real problem but many patients continuing for more than 16 courses wanted a break ("get one week free"). Treatment delays for up to one week were then accepted. Dose reduction was performed in 11

Table 5. — *Toxicity according to WHO grading in patients with platinum-resistent disease; Group A, no. = 57.*

WHO grade	0	1	2	3	4
anemia	47	8	2	-	-
neutropenia	44	11	-	-	-
trombocytopenia	57	-	-	-	-
infection/fever	57	-	-	-	-
nausea/vomiting	57	-	-	-	-
myalgia	25	32	-	-	-
arthralgia	30	26	1	-	-
neurotoxicity	22	30	3	1	-
nails	49	5	3	-	-
hypersensitivity	57	-	-	-	-
alopecia	57	-	-	-	-
oedema	56	1	-	-	-

patients, one dose level in ten and two dose levels in one patient due to neutropenia. No bone marrow stimulation was used. Treatment was delayed for a few days in seven patients due to neutropenia and in six patients for reasons of convenience.

Discussion

In spite of the fact that up to 80% of patients with AOC will respond to modern first-line platinum- and paclitaxel-based chemotherapy, a majority of them will ultimately experience a relapse and develop drug-resistant disease. Although the treatment goal in these patients is essentially palliative, worthwhile remissions can be obtained with a variety of drugs such as topotecan [25], gemcitabine [26], oral etoposide [27] and liposomal doxorubicin [28]. Paclitaxel has been studied extensively in the setting of platinum-resistant ovarian cancer and, although different doses and schedules have been used, studies have generally reported response rates between 24 to 30% [13, 15, 29-31]. Given the fact that paclitaxel now is part of the standard first-line treatment for ovarian cancer, most patients will have tumors previously exposed and possibly resistant to paclitaxel. Since the spectrum of toxicity and possibly the mechanism of action depend on the schedule of administration of this drug, attention has been focused on exploring alternative schedules of paclitaxel administration in paclitaxel pretreated patients.

Preclinical data have suggested that the duration of exposure of cancer cells to the drug may be critical for cell kill [32, 33]. However, the promising results associated with the prolonged 96-hour infusion of paclitaxel, with a total dose of 120 to 160 mg/m^2, obtained in patients with breast cancer, could not be repeated in patients who failed on shorter infusions of paclitaxel [34]. Also, such prolonged infusion is rather inconvenient for patients receiving palliative treatment. An alternative method of increasing drug exposure is delivery of the drug on a more frequent dosing schedule. Such a strategy of dose-dense therapy could be especially interesting in the case of a cell cycle specific drug such as paclitaxel [35]. In addition, shorter treatment intervals may allow less opportunity for the emergence of drug-resistant cell clones. Also, more frequent exposure to paclitaxel might increase the drugs anti-angiogenic effects [36].

Based on this rationale and on the promising results from other studies, [16-18, 37], we performed a phase II study of the weekly administration of 80 mg/m^2 paclitaxel in platinum-resistant patients with epithelial ovarian cancer. Thirty-nine of the 57 patients included in the study also had disease resistant to a standard three-weekly paclitaxel scheme. The response rates observed in our study (OR: 56% in 57 platinum-resistant cases; 60% in 15 platinum-refractory; 49% in 39 platinum- and paclitaxel-resistant; 38% in 8 platinum- and paclitaxel-refractory) are somewhat higher than those found in other studies [18, 37]. In all patients with elevated CA 125 (> 35 kU/l), responses were confirmed by accepted CA 125 response criteria [21, 22]. The median duration of response, 6.5 months for complete and 3.0 months for partial responders with platinum-resistant disease, was in accordance with results from most non-comparative phase II studies in this setting. Although great caution must be exercised when trying to compare individual phase II studies, the median progression-free and overall survival time for all 57 patients of 5.0 and 13.7 months respectively, with an 18-month survival probability of 41%, compares favorably with experience from other single-drug regimens [25-28]. A possible explanation for the high response rates observed in our study was that, although the time from last cytotoxic treatment to the start of weekly paclitaxel was short (≈ 1 month), the median paclitaxel-free interval was 11.5 and 6.7 months for the platinum- and platinum/paclitaxel-resistant group, respectively. Abu-Rustum et al showed that the response rates to weekly paclitaxel were higher in patients with a longer paclitaxel-free interval [37]. This could mean that an extension of the paclitaxel-free interval could increase the possibility of overcoming acquired resistance in some cases. A similar phenomenon has been observed with increasing the platinum-free interval in second-line chemotherapy of ovarian cancer [38]. Also, preclinical evidence suggests that, in ovarian cancer cell lines resistant to cisplatin, the platinum compound inhibits paclitaxel-induced apoptosis [39]. Translated to the clinic, this could mean that some patients who fail to respond to the combination actually might be paclitaxel-sensitive. Nevertheless, the observation that a significant number of responses were still obtained in the 15 heavily pretreated and platinum- and the eight platinum- and paclitaxel-refractory patients, remains promising. The possibility of obtaining a response was not related to the number of lines and type (with or without anthracyclines) of previous chemotherapy, stage, grade or histology.

Given the fact that treatment for relapsed or persistent ovarian cancer is essentially palliative, its cost in terms of quality of life (QoL) is very important. Although no formal QoL measurements were performed in this study, an analysis of the toxicity data in these heavily pretreated patients is very encouraging. No cases of grade 3 or 4 myelotoxicity were noted. The treatment was very well

tolerated without any cases of hypersensitivity or hospital admissions for treatment-related complications. The principal toxicity was non-hematologic (myalgia, arthralgia and neurotoxicity) but most cases were of grade 1 or 2 severity. With regard to neurotoxicity, only one patient experienced a progression of a pre-existing grade 2 to grade 3 toxicity. The typical discoloration of finger nails and toenails associated with the weekly administration of paclitaxel was mild and occurred only in 14% of the patients.

Conclusion

In conclusion, analysis of the data from this phase II study show that the weekly administration of paclitaxel is associated with a very promising response rate in patients with platinum- and paclitaxel-resistant or refractory ovarian cancer. The favorable toxicity profile with minimal non-cumulative hematologic and non-hematologic toxicity makes this treatment a valuable addition to the therapeutic options for patients with platinum- and paclitaxel-resistant ovarian cancer.

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