Weekly paclitaxel in the treatment of recurrent ovarian carcinoma

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Summary

Purpose: To study the effect of weekly paclitaxel in the treatment of recurrent ovarian and peritoneal carcinoma. *Methods:* A retrospective analysis of patients treated at Christie Cancer Centre between May 2003 and May 2005 was carried out. *Results:* Forty-nine patients with recurrent ovarian and peritoneal carcinoma were treated. The mean duration of treatment was 11 weeks, with 27 (54%) patients receiving 12 or more treatments. The most frequent non-haematological toxicities reported were mild nausea, constipation, lethargy and neuropathy. Moderate anaemia was noted in 50% of patients. Radiological assessment by CT scanning showed that complete or partial responses were achieved in 28% of patients. CA125 response was demonstrated in 63% of patients. Median time to recurrence was 149 days and median survival was 359 days. *Conclusion:* This study provides evidence for the role of weekly paclitaxel in the treatment of recurrent ovarian and peritoneal carcinoma even in a drug-resistant setting following multiple lines of prior therapy.

Key words: Paclitaxel; Recurrent ovarian carcinoma; Recurrent peritoneal carcinoma.

Introduction

Ovarian carcinoma is the fourth most common cancer in women and the leading cause of death from gynaecological malignancies [1]. As many as 60-70% of patients present with advanced stage disease and the prognosis for these women is poor [2]. A multimodality approach, with cytoreductive surgery followed by platinum-based chemotherapy, is the mainstay of treatment.

The introduction of paclitaxel as an active agent in ovarian cancer represents an important adjunct to the traditionally used platinum therapies. The mechanism of action of paclitaxel is to promote the assembly of microtubules and stabilization of tubulin polymers thus inhibiting cell division and blocking cells in the G2/M phase of the cell cycle [3]. *In vitro* data suggest that the duration of exposure to paclitaxel plays a critical role in the cytotoxic efficacy [4]. Prolonged exposure to a relatively low concentration of the drug has been shown to have anti-angiogenic properties [5] as well as inducing apoptotic cell death [6]. This provides the rationale for weekly administration of paclitaxel where, compared to standard three-weekly dosing, there is more sustained exposure of dividing tumour cells to its cytotoxic effects while lowering the maximum concentration of drug to which the patient is exposed and thereby reducing toxicity [7]. This dose-dense approach may inhibit tumour regrowth between cycles and limit the emergence of malignant cell populations resistant to chemotherapy [8]. In addition it has been reported to result in anti-angiogenic effects and tumour dormancy [9, 10].

Patients with advanced stage ovarian cancer have a response rate of between 73 and 77% to first-line chemotherapy, with a median progression-free interval of 16-18 months, and a median survival of 35-38 months [11]. The response rate to a second-line therapy is significantly less than for first-line treatment, in the region of 20% [12]. With this in mind, efforts are being made to increase the response to chemotherapy in relapsed disease and to maintain any response for as long as possible. This study investigated weekly paclitaxel in relapsed disease as one regimen that may be of value in this context.

Materials and Methods

All patients with either recurrent ovarian or primary peritoneal carcinoma who were treated with weekly paclitaxel at Christie Cancer Treatment Centre between May 2003 and May 2005 were identified. Their notes were retrieved and reviewed.

Paclitaxel was administered on a weekly basis at a dose of 70 mg/m^2, given as a one-hour infusion, in an outpatient setting. Patients were premedicated with 10 mg of dexamethasone and 50 mg of ranitidine for the first week only. Ondansetron (8 mg) was given as an antiemetic. Thereafter the dose of dexamethasone was reduced by 2 mg a week until the patients did not receive any corticosteroid premedication.

During therapy, toxicity was assessed according to GOG scoring systems. Staging CT scans were performed, where possible, before treatment and subsequently at six weekly intervals. Serum CA125 was assessed prior to treatment and thereafter at each visit. Clinical response was assessed both according to CA125 as defined by GCIG [13], and radiologically [14].

Complete radiological response was defined as the total disappearance of all measurable tumours on CT scan. Partial radiological response was a 50% reduction in the sum of the two perpendicular diameters of all measurable tumours on CT scan. Disease progression was defined as appearance of new lesions or an increase of more than 50% in the sum of two perpendicular diameters of an existing lesion. Stable disease was defined as any response that fell between progression and partial response.

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Results

A total of 49 patients were included in this retrospective analysis. A further nine patients were identified who commenced weekly paclitaxel. However, treatment was withdrawn within four weeks of therapy and as such they were not included in the final analysis. Reasons for withdrawal included acute anaphylaxis (n = 2), severe myelosuppression (n = 1), disease progression (n = 2) and acute deterioration in health (n = 4).

Of the 49 patients assessed, 41 (84%) had recurrent ovarian carcinoma and eight (16%) had recurrent peritoneal disease (Table 1). The mean age at the time of weekly paclitaxel therapy was 64.5 years (range: 43-81 years). Most patients had advanced stage disease, with 41 (84%) patients having FIGO Stage III or IV disease. Prior to first-line chemotherapy 30 (62%) patients had undergone debulking surgery. A further nine (18%) patients had second-look laparotomies and debulking surgery following one course (6 cycles) of chemotherapy. Ten (20%) patients had a diagnostic biopsy only.

Weekly paclitaxel was not first-line chemotherapy for any of the 49 patients in this study, and was second- or third-line therapy for the majority (Table 1). The median number of prior chemotherapy regimens received was 2.3. Twenty-six of the 48 patients previously exposed to platinum chemotherapy were defined as having platinum-resistant disease, while six had platinum refractory disease. Five of the 22 patients previously exposed to paclitaxel had paclitaxel resistant disease and two had disease that was paclitaxel refractory. Four patients had disease that was resistant to both platinum and paclitaxel. Thus in total 35 (71%) of patients had disease that was resistant to one or more agents and a further eight (16%) patients had disease that was refractory to previous therapy.

During treatment with weekly paclitaxel four patients required a dose reduction. Treatment was deferred for between one and two weeks in six (19%) patients and withdrawn in 17 patients before 12 weeks. In the majority of cases withdrawal of treatment was because of clinical evidence of disease progression (n = 12), but in three cases it was as a result of grade 3 peripheral neuropathy. Two of these patients had suffered peripheral neuropathy (grade 2/3) on exposure to conventional paclitaxel therapy, and had grade 1 residual symptoms at the start of weekly treatment.

Toxicities experienced during weekly paclitaxel are further described in Table 2. The most frequent non-haematological toxicities reported were mild nausea, constipation, lethargy and neuropathy. Moderate anaemia (between 8-10 g/dl) was noted in 50% of patients on weekly paclitaxel. Of these, 19 patients required a blood transfusion during chemotherapy. In addition, three patients developed a rash, although in all cases this was mild and did not necessitate discontinuation of treatment.

The mean duration of treatment was 11 weeks (range: 5-19 weeks), with 27 (54%) patients receiving 12 or more treatments. Response to weekly paclitaxel was

Table 1. — *Patient characteristics.*

	Number	Percentage (%)
Histology		
Peritoneal	8	16
Ovarian		
Serous	17	36
Endometrioid	8	16
Granulosa	1	2
Clear cell	10	20
Transistional	1	2
Carcinosarcoma	3	6
Unknown	1	2
FIGO stage		
I	5	10
II	3	6
III	33	68
IV	8	16
Number of prior regimens		
One only	11	22
Two	15	31
Three	15	31
Four	6	12
> Four	2	4
Chemotherapy resistance status		
Platinum resistant	26	54
Platinum refractory	6	13
Paclitaxel resistant	5	23
Paclitaxel refractory	2	9
Platinum and Paclitaxel resistant	4	18
Total chemotherapy resistant	36	73
Total chemotherapy refractory	8	16

Table 2. — *Toxicity profiles.*

Toxicity		Number	Percentage (%)
Non-haematological			
Nausea:	Grade 1	11	22
	Grade 2	3	6
Vomiting	Grade 1	4	8
	Grade 2	2	4
Diarrhoea:	Grade 1	4	8
	Grade 2	3	6
Constipation:	Grade 1	5	10
	Grade 2	3	6
	Grade 3	1	2
Alopecia:	Grade 1	3	6
	Grade 2	2	4
Myalgia:	Grade 1	5	10
	Grade 2	3	6
Lethargy:	Grade 1	13	27
	Grade 2	8	16
Hypotension:	Grade 3	1	2
Neuropathy:	Grade 1	14	29
	Grade 3	5	10
Haematological			
Leucopenia:	Grade 1	10	20
	Grade 2	7	14
	Grade 3	2	4
Anaemia:	Grade 1	11	22
	Grade 2	26	50
	Grade 3	1	2
Thrombocytopenia:	Grade 2	1	2
	Grade 3	1	2

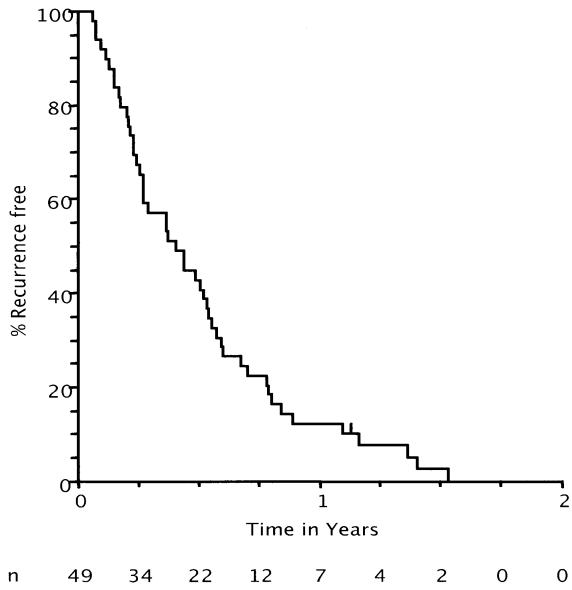

Figure 1a. — Kaplan Meier curve showing time to disease recurence.

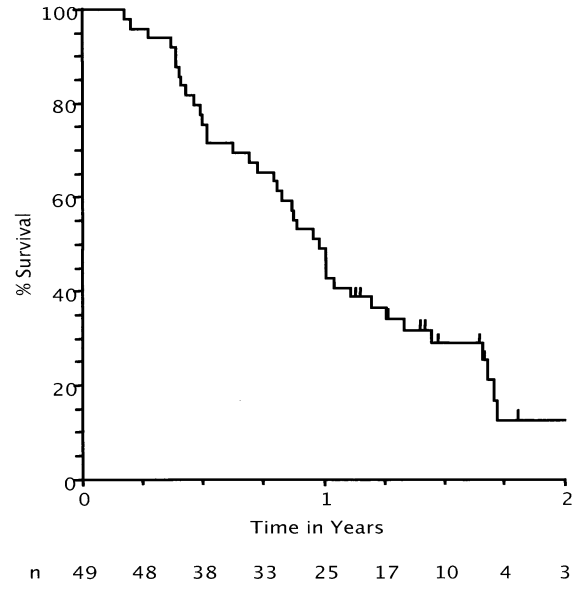

Figure 1b. — Kaplan Meier curve showing survival.

Table 3. — *Response to treatment, as assessed by CA125 level (CGIG criteria) and CT scan.*

	Number	Percentage (%)
CA125 levels		
Response	31	63
No response	5	10
Not evaluable	13	27
CT scan responses		
Complete	2	4
Partial	12	24
Stable disease	16	33
Disease progression	18	37
Not applicable	1	2

assessed by CT scan and CA125 serum levels. Results are shown in Table 3. CA125 measurement was not helpful in 14 patients, whose tumours produced very low levels (< 25 IU/l). CA125 response was documented in 63% of patients. Using computed tomography (CT) scan assessment, complete or partial response was achieved in 28%, with disease stability in 33%.

Response (using CT criteria) was assessed against several variables in an attempt to identify factors predictive for response. These included age at diagnosis/treatment with weekly paclitaxel, stage at diagnosis, disease extent at start of weekly paclitaxel (extent of local disease, distant metastases and ascites), number of cycles of paclitaxel received and/or the number of previous treatment regimens received prior to weekly paclitaxel. No significant correlation was found between any of the variables and disease response. Similarly there was no significant correlation between complete or partial CT-based disease response and either the platinum-free interval (mean value 164 days, range 7-80 days) or the treatment-free interval (mean value 79 days, range 0-680 days).

Median time to recurrence for the 49 patients was 149 days (Figure 1a) and median survival was 359 days (Figure 1b). Of those with disease progression three received further chemotherapy. The remaining 18 patients died from progressive disease.

Discussion

This study examined the effect of weekly paclitaxel in 49 women with recurrent ovarian and peritoneal carcinoma. The conventional dose of paclitaxel is 175 mg/m^2 given every three weeks. Several investigators have examined the use of paclitaxel in a weekly schedule in order to expose dividing tumour cells to a more sustained level of the drug while reducing toxicity compared to the three-weekly regimen. Fennelly *et al.* carried out a phase I trial of weekly paclitaxel in 1997. They treated 18 patients with platinum and paclitaxel resistant ovarian cancer and determined that 80 mg/m^2 was the maximally tolerated dose [15], producing a response rate of 30%. A follow-up study by Abu-Rustum *et al.* [16], looked at 45 patients with recurrent ovarian cancer. Weekly paclitaxel was administered at doses between 60 and 100 mg/m^2; resulting in a similar response rate (28.9%). In a further study by Markman and colleagues, 48 patients with chemoresistant ovarian and peritoneal cancer were given paclitaxel at a weekly dose of 80 mg/m^2 [17] with an observed objective response rate of 20.9%. In this study a dosage regimen of 70 mg/m^2 was used with a response rate of 28%, based on CT criteria.

An important factor when selecting chemotherapy regimens for recurrent ovarian carcinoma is the maintenance of quality of life. The toxicity profile of any regimen is therefore extremely important. White cell counts begin to fall five to seven days after administration of paclitaxel, with a nadir generally being reached between day 7 and 14. This fall can be reduced by prophylactic administration of granulocyte colony-stimulating factor (GCSF), however, weekly scheduling offers a clinical alternative for the minimisation of myelosuppression [18]. Severe neutropenia has only been reported in between 3% and 15% of patients receiving weekly infusions [15, 16], and in 4% (2 patients) in this report. Moderate anaemia (8-10 g/l) was noted in as many as 26 patients (50%). Because this cohort of patients would be at high risk of anaemia whether or not they were receiving chemotherapy it is difficult to assess what impact the paclitaxel had on the degree and frequency of anaemia.

The severity and frequency of peripheral neuropathy associated with paclitaxel may be related to infusion times in addition to dose, with more rapid infusions being associated with higher incidences. The neuropathy typically manifests initially as a burning or tingling sensation in the glove and stocking areas and can progress to motor weakness with continued administration of the drug [19]. While a frequently reported side-effect with weekly regimens, symptoms are usually mild to moderate (29% in this study). Severe neuropathy, affecting function, has however, been recognised in the literature (8-10%), and affected five patients (10%) in this study. These symptoms were reported between eight and 11 weeks of therapy and a dose reduction of 25% was initially introduced. However, symptoms were not alleviated and treatment had to be withdrawn in all five patients. For three of whom this was before 12 weeks of therapy. Two of the five patients had previously suffered peripheral neuropathy (grade 2/3) on exposure to conventional paclitaxel therapy, and had grade 1 residual symptoms at the start of weekly treatment.

Hypersensitivity reactions (HSR) can occur on exposure to paclitaxel, and dexamethasone and histamine antagonists have been employed as premedications for prophylaxis against such reactions. Frequent administration of premedications for weekly paclitaxel are themselves associated with side effects. Quock *et al.* confirmed a 4% risk of HSR upon first exposure, but rarely on repeat exposure. They concluded that premedication (with 10 mg dexamethasone, 300 mg cimetidine, and 25 mg diphenhydramine), in the absence of HSR, was therefore, only required before the first cycle [20]. In this study 10 mg dexamethasone and 50 mg ranitidine were given as premedication before the first exposure only. Thereafter the dose of dexamethasone was reduced by 2 mg per week until the patients did not receive any corticosteroid premedication. Two patients experienced acute shortness of breath on first exposure which was sufficient for the treatment to be withdrawn and they were excluded from the final study group. In addition, four patients developed a mild rash after repeated exposures, but this was not severe enough to affect their treatment.

In this study there was a response rate of 28% by radiological assessment and 63% by CA125 measurement. This substantial difference in response rates is consistent with previous data [21] and several possible explanations exist for the finding. For example, measuring CA125 levels may be a more sensitive way of detecting a response in disease that is not easily detected on a CT scan such as for lesions less than 1 cm in size. A second possible explanation may relate to the anti-angiogenic mechanism of action of paclitaxel when used in a weekly regimen. This may be more likely to induce a cytostatic rather than a cytotoxic effect which may be reflected in falling CA125 levels without a radiological response as defined by standard radiological criteria.

None of the many variables studied influenced response to weekly paclitaxel. Recent data by Kita and co-workers indicated that weekly paclitaxel was more effective in patients with longer platinum-free intervals [21]. In addition clinical response was indirectly correlated to number of prior regimens; as the number of prior regimens increased the response to paclitaxel decreased. This could not be demonstrated in our study although, compared to Kita, our patients were much more heavily pre-treated, 77% of the patients having received two or more courses of chemotherapy prior to weekly paclitaxel.

Conclusion

The treatment of recurrent ovarian and peritoneal cancer is a challenging problem. The majority of patients who initially respond will eventually develop chemotherapy-resistant disease and ultimately die. Treatment objectives are therefore to prolong remission and maintain quality of life. This study shows an overall radiological response rate of 28% and a CA125 response rate of 63%. The median time to recurrence for the 49 patients was 149 days and median survival was 359 days. The therapy was generally well tolerated, although the risk of grade 3 neuropathy is noted, particularly in patients who had previously experienced neuropathy with conventional paclitaxel. The documented responses in conjunction with an acceptable toxicity profile support further investigation of this regimen as part of a prospective trial. Other approaches include the use of such regimens earlier in the natural history of the disease. Alternatively dormant cancer cells, undetected at the end of first-line chemotherapy, might remain sensitive to paclitaxel following surgical-chemical cytoreduction. It may be that a combination of high-dose platinum-based standard drug administration, followed by weekly paclitaxel-based infusions could afford further treatment benefit with acceptable toxicity profiles.

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