Pergamon

European Journal of Cancer Vol. 33, No. 3, pp. 379–384, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00484-4

Original Paper

Extended Phase II Study of Paclitaxel as a 3-h Infusion in Patients with Ovarian Cancer Previously Treated with Platinum

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An extended phase II study was performed to evaluate single-agent paclitaxel as salvage chemotherapy for ovarian cancer. The aim of this study was to evaluate the 3-h infusion schedule of paclitaxel in terms of toxicity and antitumour efficacy. Furthermore, we analysed the impact on response and survival of the extent of prior chemotherapy and status of resistance against platinum. This study was an open, non-randomised, multicentre trial. The dose of paclitaxel used was 175 mg/m^2 in patients who had received one or two prior therapies, and 135 mg/m^2 in patients who had received three prior therapies. Paclitaxel was given as a 3-h infusion. Courses were repeated every 3 weeks. 114 patients with platinum-pretreated epithelial ovarian cancer were recruited of whom 112 were found eligible and evaluable for toxicity. 104 patients with bidimensionally measurable disease who received more than one course of chemotherapy were evaluable for response, progression-free (PFS) and survival. Toxicity was generally manageable. Main toxicities were non-cumulative neutropenia with 22.3% of courses with WHO grade 3/4 and peripheral neuropathy which occurred in more than half of the courses and was of WHO grade 2 and 3 in 20.1 and 1.3% of the courses, respectively. Neuropathy was associated with the higher dose per course and with cumulative paclitaxel dose. Objective responses were reported in 20% (21/104) of the patients (95% CI 13–29%) with a median response duration of 36.7 weeks. Survival and PFS for the whole group were 45.9 and 15.1 weeks, respectively. Performance status, number of tumour lesions and extent of prior chemotherapy were found to be prognostic factors for survival. Extent of prior chemotherapy was the only prognostic factor for PFS. Platinum resistance did not predict response to treatment. Paclitaxel 175 mg/m^2 given as a 3-h infusion is an appropriate treatment for patients with platinum-resistant ovarian cancer who have not previously received more than two chemotherapy regimens. Paclitaxel did not show results superior to historical data for platinum retreatment in patients with platinum-sensitive, recurrent ovarian cancer. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: ovarian neoplasms, paclitaxel, salvage therapy, recurrence, platinum resistance

Eur J Cancer, Vol. 33, No. 3, pp. 379–384, 1997

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Received 12 Jul. 1996; revised 19 Sep. 1996; accepted 18 Nov. 1996.

INTRODUCTION

OVARIAN CANCER is the sixth leading cause of cancer morbidity and the fifth leading cause of cancer mortality among

European women [1]. The majority of patients are diagnosed with advanced stage disease. Standard first-line treatment of advanced ovarian cancer consists of radical debulking surgery followed by platinum-containing combination chemotherapy [2]. Although treatment results in high response rates, the majority of patients will ultimately die from ovarian cancer. Five-year survival rates in Europe are 25–30% [1]. Due to the considerable high failure rate of primary chemotherapy, development of effective second-line treatment is of clinical relevance.

Patients who are not cured by first-line therapy can be separated into at least two subgroups with distinct prognosis. The classification of these two subgroups is based on the time-to-treatment-failure and the response to platinum-based first-line therapy (modified from [3]). The first group includes patients who are considered to have platinum-sensitive recurrent tumours; they show at least a partial response to platinum therapy and the time-to-treatment-failure exceeded 6 months after cessation of first-line chemotherapy. The second group with a worse prognosis is considered to suffer from platinum-refractory tumours; they fail to respond to first-line therapy (primary platinum resistance) or relapse within 6 months after platinum first-line therapy (secondary platinum resistance). These two groups differ significantly according to prognosis, although none of these patients will definitively be cured and treatment for both recurrent and refractory ovarian cancer is strictly palliative.

Platinum rechallenge can be considered as appropriate treatment for recurrent, platinum-sensitive ovarian cancer [4] and response rates of 25–43% have been reported [5–7].

The prognosis of patients with platinum refractory ovarian cancer is poor and most available cytostatics fail to show remarkable efficacy in these patients. Paclitaxel is the first cytostatic drug that has been shown to be active even in platinum refractory ovarian cancer. In five phase I/II studies of paclitaxel at doses of 135–300 mg/m^2 as a 24-h infusion, a total of 815 patients with platinum-refractory ovarian carcinomas have been enrolled [8–12]. One hundred and eighty-six objective responses (22.8%) have been observed among these patients. These results have led to the NIH Consensus Statement that "for a woman with recurrent ovarian cancer resistant to platinum who has not received paclitaxel, paclitaxel is the best salvage therapy currently available" [13].

A European–Canadian multicentre trial has shown, for the first time, that a reduction of the infusion time to 3 h does not compromise efficacy [14]. Furthermore, the shorter infusion schedule induced significantly less myelosuppression while making feasible the administration of paclitaxel in an outpatient setting.

Some of the contributors to the European–Canadian study (A.dB, K.B, H.G.M., C.S.) together with four different centres in Germany decided to evaluate further the 3-h schedule of paclitaxel in patients with platinum-pretreated ovarian cancer. Furthermore, the role of paclitaxel as third- and fourth-line therapy was also evaluated.

PATIENTS AND METHODS

This study was conducted as a non-randomised, open multicentre trial in seven institutions in Germany and Switzerland. The study was performed according to the GCP guidelines and according to the regulations of local ethics committees. Toxicities were graded according to the WHO classification and tumour response was reported according to the UICC guidelines [15]. Inclusion criteria were as follows: histologically proven epithelial ovarian cancer; at least one and a maximum of three previous chemotherapy regimens, of which at least one had to contain a platinum compound; bidimensionally measurable disease; adequate bone marrow (i.e. absolute neutrophil count $\geqslant 1.5 \times 10^9$/l and thrombocyte count $\geqslant 100 \times 10^9$/l), renal (serum creatinine $\leqslant 1.25 \times$ upper limit) and hepatic function (bilirubin $\leqslant 1.25 \times$ upper limit); Eastern Cooperative Oncology Group performance status $\leqslant 2$; and life expectancy $\geqslant 12$ weeks. Patients were excluded in case of: second malignancy (except non-melanoma skin cancer or surgically cured carcinoma *in situ* of the cervix uteri); history of myocardial infarction; clinical signs of congestive heart failure; history of second- or third-degree heart block or other atrial or ventricular arrhythmias, even if medically controlled; pre-existing neuropathy >WHO grade 1; history of allergic reactions against the study treatment; concomitant chemo-, radio-, endocrine or immunologic therapy within 4 weeks prior to study entry; and mental disorders and other severe illness that would hamper protocol treatment and follow-up.

Treatment consisted of paclitaxel 135 mg/m^2 in patients with three prior chemotherapies and 175 mg/m^2 in patients with one or two prior chemotherapies. Rechallenge with the same regimen was counted as two separate therapies. Paclitaxel was diluted in 1000 ml normal saline and infused over 3 h using 20 μ in-line filtration. Paclitaxel (Taxol) was provided by Bristol-Myers Squibb. Premedication consisted of 20 mg dexamethasone given orally 12 and 6 h before paclitaxel administration. H_1 and H_2 antagonists were given intravenously 30 min before paclitaxel. The most commonly used histamine antagonists were clemastine 2 mg and ranitidine 50 mg. Treatment was repeated every 21 days until progressive disease was diagnosed, or for at least two courses following an objective response. Patients who showed progressive disease while on treatment were withdrawn from the study.

No cardiac monitoring was performed, but ECG tracing was performed at baseline and at the end of treatment. Complete blood counts were repeated weekly. Non-haematological toxicities were assessed before each cycle. Treatment was delayed until haematological recovery was documented (i.e. absolute neutrophil count $\geqslant 1.5 \times 10^9$/l and thrombocyte count 100×10^9/l). No G-CSF was given prophylactically.

Patients who received at least two courses of paclitaxel were evaluable for response. Response evaluation was performed after every other course. Methods used for response assessment included bimanual gynaecological examination, ultrasound, CT scans and other radiological procedures found appropriate at baseline evaluation. CA-125 as well as clinical examinations alone were not accepted as appropriate diagnostic methods.

Statistical comparisons are based on the logrank test and relative risks are calculated from the hazard ratios. Correlation was calculated by the Spearman's correlation coefficient. Survival was calculated from the date of the first paclitaxel course to death, progression-free survival (PFS) was calculated for all patients from the first treatment course to the date on which progressive disease or recur-

Table 1. Patients' characteristics

Patients/courses	112/621
Mean age (years)	55 (27–74)
Performance status	
ECOG 0	52 (46%)
ECOG 1	50 (45%)
ECOG 2	10 (9%)
No. of disease sites	
1	36 (32%)
2	39 (35%)
>3	37 (33%)
Ascites	43 (38%)
Pleural effusion	16 (14%)
Prior CT regimens	
1	35 (31%)
2	43 (38%)
3	34 (30%)
Prior radiotherapy	11 (10%)
Prior endocrine therapy	11 (10%)
Interval from first platinum treatment	8.8 months (1–63 months)
Platinum-sensitive disease	39 (35%)
Platinum-refractory disease	73 (65%)

rence or death, whichever occurred first, was diagnosed. Response duration was calculated only for patients who achieved an objective response (OR); i.e. complete response (CR) or partial response (PR) and was calculated from the first paclitaxel course until progression or death.

RESULTS

Of 114 patients enrolled, 112 patients received 621 chemotherapy courses. Two patients did not start treatment and were excluded from the analysis. All patients and courses were evaluable for toxicity and 104 patients, who received more than 1 course, were evaluable for response and survival.

All patients were heavily pretreated and two-thirds received the study medication as third- or fourth-line chemotherapy (Table 1). Median number of measurable tumour lesions was two (range 1–5), and ascites was present in 38% of the patients. Two-thirds of patients were classified as having platinum refractory disease. Thirty-five per cent of patients suffered from recurrent disease. The mean interval between the last platinum chemotherapy and start of paclitaxel for the whole study population was 8.8 months (1–63 months).

Toxicity

Haematological toxicity was generally manageable. The main toxicity was neutropenia with 22.3% of courses accompanied by WHO grade 3 or grade 4 neutropenia. The higher paclitaxel dose induced a slightly higher incidence of WHO grade 3/4 neutropenia (Table 2). Longitudinal analysis in the subgroup of patients receiving paclitaxel 175 mg/m^2 over 10 subsequent courses did not reveal cumulative neutropenia. Furthermore, myelosuppression did not induce relevant treatment delay. The median treatment interval of 21 days remained unchanged over 10 subsequent courses as did the proportion of courses which had to be delayed for more than 7 days (7.9% and 10.5% in the first and tenth course, respectively). Thrombocytopenia and anaemia WHO grade 3 or grade 4 were rare.

Table 2. Haematological toxicity (per cent of courses) in patients receiving paclitaxel salvage therapy 135 mg/m^2 or 175 mg/m^2

	135 mg/m^2		175 mg/m^2	
WHO grade	3	4	3	4
Anaemia	2.3	0.3		0.6
Thrombocytopenia	0.6			
Leucopenia	12.4	0.6	11.7	0.4
Neutropenia	8.6	7.9	16.6	6.2

Table 3. Non-haematological toxicity (per cent of courses) in patients receiving paclitaxel salvage therapy 135 mg/m^2 or 175 mg/m^2

	135 mg/m^2		175 mg/m^2	
WHO grade	3	4	3	4
Hypersensitivity reaction	0.6		0.4	
Alopecia	85.7		86.1	
Pain/myalgia/arthralgia	1.3		3.3	
Neuropathy	0.6		1.5	
Constipation			0.2	

Non-haematological toxicity consisted mainly of total alopecia and myalgia/arthralgia. The latter rarely exceeded WHO grade 2. Again, the higher dose induced only a slightly higher incidence of non-haematological toxicities (Table 3). Other rare non-haematological toxicities included hypersensitivity reactions of WHO grade 2 or 3; oedema, diarrhoea, tinnitus, phlebitis, conjunctivitis, vertigo, Morbus Raynaud-like symptoms and angina pectoris-like symptoms. Neurotoxicity WHO grade 1 or grade 2 was reported in 30.5 and 20.1% of the courses; neurotoxicity included paresthesia, numbness and burning sensations, which were typically limited to the hands and feet. WHO grade 3 neurotoxicity was reported in only 1.3% of the courses. The observed incidence of neurotoxicity was attributed to paclitaxel because less than 5% of the patients reported WHO grade 1 neuropathy at study entry. Figure 1 shows the course of neurotoxicity in patients who received 175 mg/m^2 paclitaxel. The frequency of neurotoxicity increased slightly from course 1 to course 6 corresponding to 1050 mg/m^2 of paclitaxel. After the sixth course, frequency of neurotoxicity reached a table plateau of almost 30% WHO grade 2/3 and additionally 30–40% WHO grade 1 (Figure 1). The majority of patients reported an improvement of paresthesia

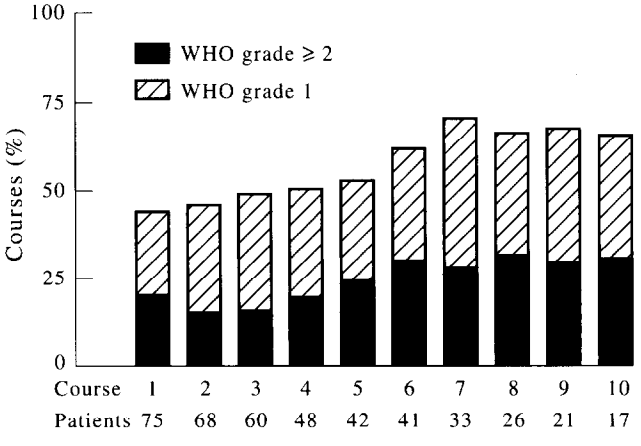

Figure 1. Severity and frequency of neuropathy over 10 subsequent courses with paclitaxel at 175 mg/m^2.

Table 4. Antitumour efficacy

	All pts (n = 104)	Refractory disease* (n = 65)	Recurrent disease† (n = 39)	Second-line (n = 29)	Third-line (n = 42)	Fourth-line (n = 33)
Complete response (%)	5	3	8	3	7	3
Partial response (%)	15	18	10	17	21	6
Overall response (%)	20	21	18	21	29	9
(95% confidence interval)	(13–29)	(12–34)	(8–34)	(8–40)	(16–45)	(2–24)
Stable disease (%)	42	41	45	48	40	42
Progressive disease (%)	37.5	38	37	31	31	48
Response duration (weeks)	36.7	33.4	37.3	42.2	33.4	37.3
(Range)	(1–151)	(20–108)	(15–151)	(15–151)	(4–151)	(27–68)
Progression-free survival (weeks)	15.1	17.7	14.7	21.7	17.4	9.6
(Range)	(1–151)	(1–108)	(3–151)	(4–151)	(3–67)	(1–68)

* Refractory disease: best response to platinum was a stable disease or relapse occurring within 6 months after the last platinum therapy (independent of whether the patient received a non-platinum-containing therapy thereafter). † Recurrent disease: best response to platinum was at least a partial response and recurrence occurring later than 6 months following the last platinum therapy

within 3–6 months after the end of paclitaxel. The comparison between patients receiving paclitaxel at a dose of 175 mg/m^2 or 135 mg/m^2 did not show a significantly different toxicity profile, but the higher dose was associated with a slightly higher incidence of neuropathy.

Tumour response and response duration

The mean observation period in the 104 patients evaluable for response was 163 weeks (median 145 weeks). At the time of this report, all but 1 patient had experienced disease progression or recurrence and all but 28 patients had already died. The overall response rate was 20% (21/104) (95% CI 13–29%) with 5% (5/104) of patients achieving a complete response (Table 4). Median response duration was 36.7 weeks (15–151 weeks). Progressive disease was observed in 37.5% (39/104) of patients and did not differ significantly between patients with platinum-refractory or platinum-sensitive tumours. Response rates did not differ significantly between patients who received paclitaxel as second-line or third-line therapy. In contrast, results in patients receiving paclitaxel as fourth-line treatment were inferior. Nearly half (48%) of these patients showed progressive disease whilst on treatment, and less than 10% achieved an objective response.

Survival analysis and prognostic factors

The median survival for the whole group was 45.9 weeks from study entry. Performance status, presence of ascites, numbers of tumour lesions (>two lesions) and extensive pretreatment (>two prior regimens) were found to be risk factors for survival (Table 5). Performance status and presence of ascites were significantly correlated (r = 0.275; P = 0.0048), while performance status and numbers of tumour lesions were not (r = 0.046; P = 0.64). Stepwise analysis revealed the highest efficacy in patients who presented with a performance status of less than ECOG 2 and less than three measurable tumour lesions. The 82 patients who fulfilled the aforementioned criteria for a low risk status (ECOG 0–1, <three lesions) were analysed separately and stratified for resistance status and for extent of prior treatment. 30 patients had platinum-sensitive tumours and 52 platinum refractory tumours; survival was 74.1 weeks in the first group and 42.9 weeks in the latter group, respectively (P = 0.054; relative risk 1.75). 25/82 patients had received paclitaxel as second-line 34 as third-line, and 23 as fourth-line chemotherapy. Median survival did not differ substantially between patients receiving paclitaxel as second-line or third-line therapy (59.4 weeks and 56.6 weeks, respectively; P = 0.67, RR 1.15), while patients receiving paclitaxel as fourth-line therapy, a median survival of only 28.7 weeks was achieved (P = 0.009; RR 2.13 for the comparison between second-line/third-line versus fourth-line therapy).

The median progression-free survival (PFS) was 15.1 weeks for all patients. More than two prior chemotherapies was the only significant risk factor for PFS (RR 1.76, P = 0.025). Resistance against platinum showed an inverse but non-significant effect on PFS with a PFS of 17.7 weeks in patients with platinum-refractory tumours and of 15.1 weeks in patients with platinum-sensitive tumours (P = 0.52; RR 0.86). More than two prior chemotherapy regimens remained a significant prognostic factor even in the low risk group with a PFS of 9.1 weeks in patients who received paclitaxel as fourth-line therapy and a PFS of 20.1 weeks in patients who received it as second-line or third-line

Table 5. Risk factors for survival in patients with ovarian cancer treated with salvage paclitaxel

	n	Survival (median; weeks)	Relative risk (hazard ratio)	P-value (logrank test)
Age				
≤55 years	56	58.9	1	
>55 years	48	38.9	1.50	0.073
Performance status				
ECOG 0	49	66.9	1	
ECOG 1/2	55	35.9	2.14	0.0008
Tumour lesions				
1	53	51.9	1	
>1	51	31.1	1.54	0.057
>2	16	27.4	1.97	0.026
Ascites				
Absent	37	51.9	1	
Present	67	31.1	2.02	0.002
Prior chemotherapies				
1	29	59.4	1	
2	42	45.9	1.28	0.40
3	33	29.6	2.0	0.022
Resistance to platinum				
Sensitive	39	49.9	1	
Refractory	65	42.9	1.47	0.118

treatment ($P = 0.0043$; RR 1.99). Therefore, a number of prior chemotherapeutic treatments above two was the only risk factor associated with both poor survival and poor PFS.

DISCUSSION

Paclitaxel given as 3-h infusion has been shown to be effective as salvage treatment of platinum-pretreated ovarian cancer. In this trial, an objective response rate of 20% was observed, slightly higher than the 15.5% response rate reported by a U.K.–Irish group [16] with single-agent paclitaxel as salvage therapy in a comparable population. Our data are comparable with the overall 22.8% response rate calculated from five phase I/II trials using paclitaxel as a 24-h infusion in platinum-pretreated patients [8–12] and, therefore, confirm the findings of the European–Canadian trial that could not detect a significant benefit for a prolonged paclitaxel infusion schedule [14].

This trial supports the NIH Consensus Statement with respect to the role of paclitaxel in patients with earlier platinum exposure. Nevertheless, results are poor when the number of prior regimens exceeded two. A median survival of only 28.7 weeks and a PFS of less than 10 weeks in patients who already had three prior therapies raises the question of whether the expected benefit justifies costs and toxicities associated with paclitaxel treatment. It is unlikely that the worse results in patients receiving paclitaxel as fourth-line therapy might be attributed to the lower dose given to these patients (135 mg/m^2). A recently reported meta-analysis could not reveal a dose–response relationship for paclitaxel salvage treatment in ovarian cancer patients [17].

Overall, more than two prior chemotherapies, performance status and number of tumour lesions showed a significant impact on survival. Platinum resistance showed a trend for worse survival, but only in the low risk group of patients. None but the number of prior chemotherapies were associated with a poor PFS. In contrast, platinum resistance was associated with a slightly better PFS. This observation indirectly indicates that salvage therapy itself has only limited effects on survival, and that survival might mainly depend on risk factors which can only be slightly influenced by chemotherapy, such as performance status and number of tumour lesions. The latter factors were also identified as risk factors in the European–Canadian trial of paclitaxel salvage therapy [14]. Both factors depend to some degree on the time when diagnosis of treatment failure of first-line therapy is established; i.e. in at least some patients, a delay in diagnosis might lead to a greater number of tumour lesions and to a reduction of performance status, especially if the patient develops ascites. These data should be taken into consideration when criteria for the definition of follow-up intervals are discussed.

Planning salvage therapies for non-curable patients should clearly define realistic goals and toxicity, and therapy-related costs have to be weighed against expected benefits. Paclitaxel, given as a 3-h infusion in an ambulatory setting, is less expensive than a 24-h infusion. Nevertheless, drugs remain expensive and budget limitations become more and more important. Under these circumstances, fourth-line therapy with paclitaxel is hardly justified. Tumour control and prolongation of PFS could be achievable goals in patients with a good performance status and limited tumour burden who have not received more than two prior therapies. In the present study, platinum resistance was not a risk factor for a poor PFS and it does not seem to contra-indicate paclitaxel therapy in these patients. Patients with platinum-sensitive tumours did not show significant differences in PFS or response rates. Other group using platinum as salvage therapy have shown results comparable or even superior to our results in this particular group of patients [5–7]. Furthermore, convenience and costs favour platinum as treatment for recurrent ovarian cancer. Therefore, platinum should remain the standard treatment of platinum-sensitive recurrent ovarian cancer until randomised trials have shown an advantage for paclitaxel either as single agent or in combination therapies.

Treatment was generally well tolerated and no therapy-related death was observed. Haematological toxicity mainly consisted of uncomplicated, non-cumulative neutropenia. Neurotoxicity was observed as a major non-haematological toxicity in more than half of the patients. Severe and disabling neuropathy was rare. Dose per course and cumulative dose of paclitaxel seem to have an impact on neuropathy. The frequency of neuropathy seemed to reach a plateau beyond a cumulative dose of 1050 mg/m^2. However, a further increase of neuropathy could be missed, at least to some extent, due to significant patient withdrawal during the course of treatment, even though an increase of the severity of neuropathy in the remaining patients was not observed. Overall, paclitaxel given as a 3-h infusion in a dose range of 135–175 mg/m^2 is safe even in heavily pretreated patients.

In conclusion, the results of the present study indicate that single-agent paclitaxel should be considered an acceptable salvage treatment for patients with platinum refractory ovarian cancer and with less than three prior chemotherapies. Nevertheless, further improvement in this group of patients is still mandatory because of a remaining poor prognosis.

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Acknowledgements—The authors thank C. Vieweg (München), V. Karsch (Freiburg), G. Elser (Karlsruhe), Y.A. Harms (Hannover) and C. Klingler (Göttingen) for their assistance.