Pergamon

European Journal of Cancer Vol. 33, No. 1, pp. 160–163, 1997

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

PII: S0959-8049(96)00366-8

Short Communication

A Phase II Study of Paclitaxel in Platinum Pretreated Ovarian Cancer. A Hellenic Cooperative Oncology Group Study

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Paclitaxel was administered at a dose of 175 mg/m^2 in a 3-hour infusion every 3 weeks in platinum pretreated patients with ovarian cancer. 51 patients with a median age of 57 years entered the study. 33 (65%) presented with stage III and 18 (35%) with stage IV disease. 39 patients (76%) were previously treated with only one and 12 (24%) with two regimens. The median interval from the last previous chemotherapy was 4 months (range, 1–65). Ninety-eight per cent of the planned dose of paclitaxel was actually delivered. Overall and complete response rate was 26% (13/51) and 16% (8/51), respectively. All complete responses were observed among patients previously treated with only one regimen. Median time to progression was 10.26 months (range, 4.9–25.2+) and median survival 15.6 months (range, 1.3–27.1+). Factors influencing survival were performance status and the number of previous regimens. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: paclitaxel chemotherapy, ovarian cancer chemotherapy

Eur J Cancer, Vol. 33, No. 1, pp. 160–163, 1997

INTRODUCTION

OVARIAN CANCER patients who relapse after platinum-based, first-line chemotherapy have a relatively poor prognosis. Patients with stable or progressive disease or early relapse (i.e. within 6 months) after platinum-based first-line chemotherapy share a very poor outcome. Responses are rarely achieved by using the alternative platinum compound [1]. Other options until recently were very limited and included ifosfamide, oral etoposide and hexamethylmelamine [2]. In contrast, patients who relapse after a longer interval show a higher response rate to the initial platinum derivative, the alternative or another drug [1, 2]. Until the introduction of paclitaxel, there was no evidence that any second-line treatment had any effect on survival [3].

Paclitaxel carries a unique mechanism of action promoting microtubule assembly and thus interfering with cell division [2]. Phase II studies have indicated that it is effective even in patients considered platinum refractory [4]. The Hellenic Cooperative Oncology Group (HeCOG) conducted a phase II study in which ovarian cancer patients pretreated with platinum-based chemotherapy were treated with paclitaxel monotherapy.

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Received 29 Mar. 1996; revised 29 Jul. 1996; accepted 3 Aug. 1996.

PATIENTS AND METHODS

To be eligible for the study, patients had to have histologically confirmed ovarian cancer, either stable or progressive while on platinum-based chemotherapy, or relapsed after platinum treatment. Patients had to have measurable or evaluable disease, an ECOG performance status of 2 or lower, adequate liver and renal function, WBC > 4000/μl, platelet count > 100.000/μl and a life expectancy of >3 months. A maximum of two previous chemotherapeutic regimens was allowed, providing that these regimens included cisplatin or carboplatin. All patients had to give written informed consent. The protocol was approved by the Ethics Committee of all participating institutions and by the National Drug Organisation.

Paclitaxel was administered at the dose of 175 mg/m^2 as 3-h infusion at the clinic. All patients were given standard premedication consisting of dexamethasone 20 mg i.v. 12

and 6 h before paclitaxel administration and dimethidene maleate 4 mg and cimetidine 150 mg i.v. 30 min before the treatment. No anti-emetic therapy was given. Courses were repeated every 3 weeks.

The dose of paclitaxel was reduced when granulocytopenia had been present for ≥7 days or in case of febrile neutropenia. If the absolute neutrophil count (ANC) was <500/μl and/or platelet count < 50 000/μl, then the dose of paclitaxel was reduced to 135 mg/m^2. In case of febrile neutropenia with or without documented infection and/or severe bleeding, the dose of paclitaxel was reduced to 110 mg/m^2. The ANC should be ≥1500/μl and the platelet count ≥100 000/μl prior to the beginning of the next treatment cycle. G-CSF (Filgrastim) was given only for life-threatening conditions (i.e. febrile infectious episode). In case of grade 3 mucositis, the dose of paclitaxel was reduced to 135 mg/m^2. In case of severe neurotoxicity or symptomatic arrhythmias or AV (atrio-ventricular) block (except first degree), paclitaxel administration was discontinued.

Pretreatment evaluation included a complete medical history, physical examination, complete blood counts (CBC), biochemistry, ECG, chest X-ray and CT of the abdomen and pelvis. Further imaging methods were suggested if indicated. CBC was repeated weekly. Tumour response was assessed every three courses, unless clear evidence of progression occurred. Patients responding to the treatment or those with stable disease were treated with a maximum of 10 cycles or until progression, whichever came first, unless unacceptable toxicity occurred. Response and toxicity were classified according to WHO criteria. Time to progression (TTP), relapse-free survival (RFS) and disease-free survival (DFS) were calculated from the date that the response criteria were first met until the documentation of progression. Survival was calculated from initiation of chemotherapy. Survival, TTP, RFS and DFS curves were performed using the Kaplan–Meier method [5]. The crude relationships of various prognostic factors to survival were analysed using the log-rank [6], Breslow [7] and Tarone–Ware tests [8]. Multivariate analysis followed, using the proportional hazards model, as proposed by Cox [9], in order to analyse survival while adjusting simultaneously for the prognostic factors.

RESULTS

From February 1993 until October 1994, 51 patients entered the study. Patient characteristics are shown in Table 1.

Table 1. Patients' characteristics

Number of patients	51	%
Age		
Median	57	
Range	31–73	
Performance status (ECOG)		
0	19	37
1	20	39
2	12	24
Stage		
III	33	65
IV	18	35
Previous chemotherapeutic regimens		
1	39	76
2	12	24
Response to last previous treatment		
Complete	15	29
Partial	19	37
Stable disease	3	6
Progressive disease	12	24
Unclear	2	4
Treatment interval from the last previous regimen (patients)		
< 6 months	30	59
≥ 6 months	21	41
Treatment interval from the last previous treatment (months)		
Median	4	
Range	1–65	

Compliance to treatment toxicity

Two severe hypersensitivity reactions (HSR) were observed in 2 patients, early in the first course of paclitaxel administration, necessitating the discontinuation of treatment. Another patient stopped treatment after only 1 cycle because of severe deterioration of her general health. One additional patient refused further treatment and follow-up after two courses of chemotherapy for family reasons.

A total of 336 courses (6.6 per patient) was given. The median dose intensity of paclitaxel actually delivered was 57 mg/m^2/week accounting for 98% of the dose prescribed by the protocol (planned dose 58.3 mg/m^2/week). The median delay per patient was one day. Apart from alopecia, which was universal after 2–3 courses, the primary toxicity was leucopenia, mainly granulocytopenia (grade III–IV: 36% of patients), which was short in duration, was rarely implicated with febrile episodes (8%) and was clearly not cumulative. Thrombocytopenia was practically not seen at all (only grade I–II: 8%), as was nausea or vomiting. Arthralgia-myalgia syndrome was common as was peripheral neurotoxicity, which was rarely (10%) severe.

Response to treatment and survival

All patients were analysed on "the intention to treat" basis. 8 patients (16%) demonstrated complete response (CR) and 5 (10%) partial response (PR) (Table 2). Tumour response according to the number of previous chemotherapeutic regimens (1 versus 2) and according to the treatment interval from the last previous treatment (<6 versus ≥6 months) are also shown in Table 2. All the complete responders and 4/5 of the partial responders had previously received only one regimen. For this subgroup of patients, both the CR rate and overall response rate was higher (21% and 31%, respectively) than the total group. Regarding the treatment interval from the previous treatment, responders were distributed in both groups (24% versus 28% respectively).

At the time of the analysis, 23 patients have died of their disease. After a median follow-up of 10 months (range 1.5–27), median DFS was 15.9 months (range 4.9–16.1), median RFS was 10.7 months (range 4.9–25.2), TTP was 10.26 months (range 4.9–25.2) and median survival was 15.6 months (range 1.3–27.1).

Table 2. Response to chemotherapy

	Previous regimens (number)		Treatment interval from last previous treatment (months)		Only evaluable patients	Total number of patients	
	1	2	< 6	⩾ 6			
	$n = 39$	$n = 12$	$n = 30$	$n = 21$	$n = 47$	$n = 51$	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	95% CI
OR	12 (31)	1 (8)	7 (23)	6 (28)	13 (28)	13 (26)	13–37
CR	8 (21)	0 (0)	5 (17)	3 (14)	8 (17)	8 (16)	5.9–26.1
PR	4 (10)	1 (8)	2 (7)	3 (14)	5 (11)	5 (10)	1.8–18.2
SD	10 (26)	0 (0)	6 (20)	4 (19)	10 (21)	10 (20)	
PD	13 (33)	11 (92)	14 (47)	10 (48)	24 (51)	24 (47)	
NE	4 (10)	0 (0)	3 (10)	1 (5)	— (—)	4 (8)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, non-evaluable for response; CI, confidence intervals.

Survival was analysed according to number of previous chemotherapeutic regimens (1 versus 2), performance status (0 or 1 versus 2), stage (III versus IV) and treatment interval from the last previous treatment (< 6 versus ⩾ 6 months). There was a statistically significant difference in favour of patients who had received only one previous regimen (16.0 versus 6.9 months, $P = 0.0016$) and had a good (0 or 1) performance status at diagnosis (20.7 versus 5.3 months, $P < 0.0001$). The difference was marginally in favour of stage III disease (15.6 versus 8.4 months, $P = 0.0197$), while there was no significant difference according to the treatment interval from the previous treatment (15.3 versus 17.9 months, $P = 0.1313$). Multivariate analysis with the above variables showed performance status to be the only important prognostic factor with a very strong negative impact on survival ($P = 0.0001$).

DISCUSSION

Paclitaxel, as used in this study, proved to be efficacious in platinum pretreated ovarian cancer patients. In fact, we obtained a 26% overall response and a 16% complete response rate. These results are similar to those reported in previous studies [4, 10–14], where the doses vary from 110 to 250 mg/m^2, but more than 70% of patients received a dose equal to or less than 135 mg/m^2. Although early studies [4, 10] did not show any dose–effect relationship, recent studies utilising higher doses achieved better response rates [12]. There is only one randomised trial comparing two different dose levels (135 versus 175 mg/m^2) at two different infusion schedules [14]. A slightly higher response rate for the 175 mg/m^2 arm was observed (20% versus 15%), but this difference was not significant. However, progression-free interval was significantly longer for the higher dose group.

In our study, all the complete responders and 4/5 of partial responders had previously received only one regimen. For this subgroup of patients, both the CR rate and the overall response rate was higher. Similarly, better results have also been observed in other studies with similar patients' characteristics [11]. The majority of patients in the present study presented with no bulky disease, as these patients were followed closely because of their participation in previous clinical studies of our group. Regarding the treatment interval from the last previous regimen (< 6 versus ⩾ 6 months), responders were equally distributed in both groups. This is in accordance with the results from other studies defining response rates for cisplatin-resistant and cisplatin-sensitive patients, separately [10, 11].

The duration of response reported in previous studies has been short and varies between 4.2 and 6.2 months. Our median TTP was 10.3 months, which may be attributable to the higher CR rate and the high DFS. The survival time in previous studies is also lower (6.5–11.5 months) than the 15.6 months median survival of this study, with the exception of the GOG study (16 months) [11]. In our study, survival was positively correlated with performance status and only one previous regimen. The same correlation for performance status was indicated in the NCI study [13]. The difference according to stage was marginally in favour of stage III disease. Finally, there was no difference according to the treatment interval from the last previous treatment.

In the majority of the previous studies the drug has been given as 24-h infusion. The impact of the duration of paclitaxel infusion (24 versus 3 h) at two different dose levels has been addressed in the Canadian European Study [14]. Response rates were similar in both arms (19% and 16%, respectively). No survival differences were noted. The conclusion was that the 3-h infusion is safe and equally effective with less myelosuppression.

Most investigators are not keen to use paclitaxel in a 3-h schedule for primary treatment. The optimistic results reported with the combination of paclitaxel and cisplatin as first-line treatment were achieved with the 24-h schedule [15]. However, this is not the case for recurrent disease, where therapy is purely palliative and quality of life is a main objective. In this cohort of patients, the 3-h infusion regimen in an ambulatory care setting seems more attractive.

In conclusion, in the present study, paclitaxel given at 175 mg/m^2 as a 3-h infusion appears to be quite efficient and is well tolerated for platinum pretreated ovarian cancer patients. Future trials should focus on the definition of the optimal dosage, duration of infusion and combinations of paclitaxel with other agents.

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Acknowledgements—The authors thank Mrs Chr. Bamias for data management and Mrs M. Moschoni and Mrs E. Papakostaki for their secretarial assistance.