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Original Paper

A Phase I-II Trial of Fixed-dose Carboplatin and Escalating Paclitaxel in Advanced Ovarian Cancer

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We conducted a phase I-II study with escalating paclitaxel doses plus carboplatin at a fixed dose for previously untreated patients with advanced ovarian cancer in order to define the maximum tolerated dose. Eligible for the study were women with a histologically confirmed diagnosis of ovarian cancer stage III-IV according to the FIGO classification. In the first phase of the study, 6 patients were allocated escalating paclitaxel doses with fixed-dose carboplatin in order to establish the maximum tolerated dose. The starting dose of paclitaxel was 150 mg/m^2 given after carboplatin (300 mg/m^2) every 4 weeks for a total of six courses. The paclitaxel dose step was 25 mg/m^2 up to 250 mg/m^2. The study then progressed to a phase II trial using the maximum tolerated paclitaxel dosage reached during the escalating dose phase. A total of 27 patients entered phase I and 23 phase II. Neurotoxicity was observed in 47 patients (94%; 29 grade 1, 17 grade 2, 1 grade 3, according to the WHO classification). The intensity of neurotoxicity tended to be dose related: out of the 15 patients who received $\leqslant$200 mg paclitaxel, a total of 14 grade 1, but no grade 2 or 3 neurotoxicities, were observed. The frequency of grade 1, 2 and 3 neurotoxicity was 15, 17 and 1, respectively, in the 35 women who received $\geqslant$225 paclitaxel +300 mg carboplatin. There was no clear relationship between median WBC and platelet nadir and dose level. Among other toxicities, alopecia was observed in all 50 cases, hypersensitivity in two (4%) and myalgia in 41 (82%; 34 grade 1 and 7 grade 2). These frequencies tended to increase with the dose, but the relationship was not statistically significant. The overall response rate was 78% (39/50) with a complete response rate of 62% (31/50). In conclusion, this study suggests that carboplatin and paclitaxel can be administered safely to patients with advanced ovarian carcinoma. The maximum dose reached was 250 mg/m^2 paclitaxel and 300 mg/m^2 for carboplatin, but from a clinical point of view the maximum paclitaxel dose we would consider safe is 225 mg/m^2. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: ovarian cancer, carboplatin, paclitaxel

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INTRODUCTION

RECENT CLINICAL series and randomised trials have suggested that paclitaxel (Taxol^{TM}) is an active therapy in ovarian carcinoma. Response rates of 16–50% with doses of 135–250 mg/m^2 have been reported in refractory ovarian carcinomas, including significant activity in cisplatin-resistant ovarian cancer [1, 2]. Following these suggestions, paclitaxel has been tested as first-line treatment in advanced ovarian cancer. The Gynecologic Oncology Group's preliminary results showed that paclitaxel (135 mg/m^2) plus cisplatin (75 mg/m^2), in comparison with cyclophosphamide plus cisplatin, increased response and survival [3]. However, efficacy of paclitaxel in combination with standard doses of

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platinum compounds in the treatment of ovarian cancer is scanty and the safety and efficacy of the association of paclitaxel and carboplatin has been tested in very few studies [4, 5]. The maximum tolerated doses (MTD) of paclitaxel and carboplatin reached with cytokine support were, respectively, 225 mg/m^2 and 7.5 area under the curve (AUC) in a study conducted by Ozols and associates [4]. In this series, the rate of objective responses was 75% and the clinical complete response rate was 67% [4]. Ten Bokkel Huinink and associates evaluated the combination with escalating doses of paclitaxel (125–200 mg/m^2) and carboplatin (300–550 mg/m^2): the overall response rate was 52% with acceptable toxicity [5].

In consideration of the potential increase in activity of paclitaxel at higher dosages as first-line treatment in ovarian cancer [2, 6], it was of interest to estimate the MTD of paclitaxel in combination with carboplatin in untreated patients.

In this paper, we present the results of a phase I-II study with escalating paclitaxel doses plus carboplatin at a fixed dose for previously untreated patients with advanced ovarian cancer.

PATIENTS AND METHODS

This was an open, non-randomised trial. Eligible for admission were women with a histologically confirmed diagnosis of ovarian cancer stage III-IV, according to the FIGO classification, observed between December 1993 and March 1995 at the collaborating centres (I Clinica Ostetrica Ginecologica, University of Milan; Clinica Ostetrico Ginecologica, Universities of Pavia, Parma and Varese). At entry, all women had Karnofsky performance status $\geqslant$80, normal haematological, hepatic, renal and cardiac functions. All subjects had clinically and/or instrumentally measurable disease. Before entry, written informed consent was obtained. Each investigator obtained institutional Review Board approval of the protocol.

In the first phase of the trial, 6 patients were allocated escalating paclitaxel doses with a carboplatin fixed dose (300 mg/m^2). If no "important" adverse event occurred in one or more of the 6 patients the paclitaxel dose was increased. An "important" adverse event was defined, according to WHO grades, as follows: absolute neutrophil count (ANC) $<0.5 \times 10^9$/l lasting for more than 7 days or ANC $<0.1 \times 10^9$/l for more than 3 days; thrombocytopenia grade 4 or more; non-haematological toxicity grade 3 or more (excluding alopecia); any episode of febrile neutropenia. The protocol did not foresee G(M)–CSF support. Toxicity grade was recorded at the start of every new course or 4 weeks after the end of the last course. Platelets, haemoglobin, leucocytes plus differential counts were tested weekly. The starting dose of paclitaxel was 150 mg/m^2 and the dose step was 25 mg/m^2. We decided that 250 mg/m^2 was the maximum paclitaxel dose to be administered.

Paclitaxel was given as a 3-h intravenous infusion 3–5 min after carboplatin. Courses were repeated every 4 weeks in an outpatient setting for a total of six courses. Patients received standard premedication before each paclitaxel infusion. The trial was then to progress to a phase II trail in which paclitaxel was given at the MTD reached during the escalating dose phase.

Response was assessed by second-look laparotomy/laparoscopy and/or imaging techniques (i.e. CT scan, ultrasound, X-ray). CA 125 was assayed in all patients. Clinical and instrumental examinations were made after the third and sixth course. In case of progressive disease, the patient was taken off study. Patients with no evidence of disease and negative CA 125 after six courses underwent a second-look laparotomy. Clinical complete response was defined as complete disappearance of all clinically detectable tumour and negative CA 125 for at least two observations not less than 4 weeks apart. Pathological complete response was disappearance of the disease at histological examination assessed by at least 10 random biopsies, with negative peritoneal cytology.

Partial response was defined as a reduction in tumour size of 50% or more in measurable disease (residual tumour >1 cm). In non-measurable disease (residual tumour $\leqslant$1 cm), partial response was assessed by surgical examination with disappearance of 50% or more positive lesions. Patients with only positive peritoneal cytology were defined partial responders.

Differences in frequency of toxicity and response were tested using the chi-squared test, comparing expected and observed events, and the trend in the frequency of adverse events was tested using the Mantel test [7].

A preliminary report including some of the subjects considered in this paper has been previously published [8].

RESULTS

A total of 50 patients entered the trial. Their characteristics are summarised in Table 1. 27 took part in the escalating paclitaxel dose phase (3 received 150 mg/m^2 paclitaxel, 6 received 175, 200, 225 and 250 mg/m^2). The decision to give only 3 patients the first paclitaxel dose was based on the fact that there were already some findings that this dose was well tolerated in combination with carboplatin 300 mg/m^2 [5], and it caused no grade 2 haematological and non-haematological toxicity (with the exception of alopecia) in the present study (Tables 2 and 3). No "important" adverse event as defined by the protocol (see Patients and Methods) was observed in phase I of the trial. However, of the 6 women who received 250 mg/m^2 of paclitaxel during phase I of the trial, 2 reported grade 1 and 4 grade 2 neuroxicity. In consideration of the high frequency of grade 2 neurotoxicity in this does group, we treated the women in the phase II trial with 225 mg/m^2 paclitaxel and

Table 1. Characteristics of patients at study entry

	n (%)
Age in years, median (range)	56 (27–74)
Stage	
III	43 (86)
IV	7 (14)
Grading	
1	4 (8)
2	11 (22)
3	35 (70)
Histotype	
Serous	29 (58)
Endometrioid	5 (10)
Other	16 (32)
Residual tumour (cm)	
$\leqslant$1	14 (28)
>1	36 (72)

Table 2. Haematological toxicity according to dose level

Dose level (paclitaxel dose)	No. of patients	Haematological toxicity: Granulocytes (%)	Platelets (10^3/μl)	Haemoglobin (g/dl)
		Nadir median, range	Nadir median, range	Nadir median, range
I (150 mg/m^2)	3*	15.8 (15.7–22.1)	82 (70–99)	10.4 (8.3–10.9)
II (175 mg/m^2)	6	21.9 (10.7–32.1)	107 (45–181)	9.4 (7.7–9.7)
III (200 mg/m^2)	6	15.5 (8.4–47.0)	160 (112–279)	10.1 (8.9–10.5)
IV (225 mg/m^2)	29**	23.0 (5.0–46.3)	125 (35–250)	9.7 (6.0–12.0)
V (250 mg/m^2)	6	25 (3.0–39.6)	159 (85–257)	9.9 (8.9–11.1)

*Only 3 patients were given the first dose. **Including 6 patients in phase I and 23 in phase II of the study.

Table 3. Non-haematological toxicity according to dose level

Dose level (paclitaxel dose)	No. of patients	WHO Grade	Toxicity (WHO grading): Neurological 1	2	3	Emesis 1	2	3	Alopecia 1	2	3	Cardiac 1	2	3	Hypersensitivity 1	2	3	Myalgia 1	2	3
I (150 mg/m^2)	3*		3	—	—	1	—	—	—	—	3	—	—	—	—	—	—	3	—	—
II (175 mg/m^2)	6		6	—	—	3	—	—	—	—	6	—	—	—	—	—	—	6	—	—
III (200 mg/m^2)	6		5	—	—	3	—	—	—	—	6	1	—	—	—	—	—	4	1	—
IV (225 mg/m^2)	29**		13	13	1	4	—	—	—	—	29	4	—	—	1	—	—	15	5	—
V (250 mg/m^2)	6		2	4	—	4	—	—	—	—	6	—	—	—	1	—	—	6	1	—
Total	50		29	17	1	15	—	—	—	—	50	5	—	—	2	—	—	34	7	—

*Only 3 patients were given the first dose. **Including 6 patients in phase I and 23 in phase II of the study.

300 mg/m^2 carboplatin. No relevant difference in the haematological and non-haematological toxicity was observed among women treated with 225 mg paclitaxel during phases I and II of the trial. Thus, for the purpose of this presentation, the patients treated with 225 mg/m^2 paclitaxel and carboplatin 300 mg/m^2 who entered phase I and phase II are considered together.

Table 2 indicates the haematological toxicity at each dose. There was no clear relationship between median WBC nadir and dose. 2 patients had thrombocytopenia of less than 50 000/μl (1 patient treated with 175 mg/m^2 paclitaxel and 1 with 225 mg/m^2). Non-haematological toxicity is shown in Table 3. Neurotoxicity was the most frequent toxicity, observed in 47 patients (94%: 29 grade 1, 17 grade 2, 1 grade 3). One case of grade 3 neurotoxicity was observed in a patient treated during phase II of the study with 225 mg/m^2 paclitaxel and 300 mg/m^2 carboplatin. The intensity of neurotoxicity tended to be dose related. Of the 15 patients who received ≤200 mg/m^2 paclitaxel, there was a total of 14 grade 1 neurotoxicities, but no grade 2 or 3. Grade 1, grade 2 and grade 3 neurotoxicity arose in, respectively, 15, 17 and 1 of the 35 women who received 225 mg/m^2 or more paclitaxel plus 300 mg/m^2 carboplatin (χ^2_1 neurotoxicity grade 0–1 versus grade 2/3, high ≥225 mg/m^2 versus ≤200 mg/m^2, $P<0.05$).

Among other non-haematological toxicities, grade 3 alopecia was observed in all 50 cases, grade 1 hypersensitivity in 2 cases (4%) and myalgia in 41 (82%, 34 grade 1 and 7 grade 2) (Table 3). These frequencies tended to rise with the dose, but not significantly (χ^2_1 trend).

The mean doses of paclitaxel actually given are shown in Table 4. A total of 15 women (11 after 225 mg/m^2 of paclitaxel and 4 after 250 mg/m^2) had to reduce the planned doses for persistent grade 2 neurological toxicity (median four courses at reduction, range 4–6). One patient stopped treatment because of grade 3 neurotoxicity. 5 patients stopped treatment for progressive disease (4 after the 4th course and 1 after the 5th). The carboplatin dose was never reduced. The mean AUC value of actually administered carboplatin dose was 5.0 (range 3.3–6.8), computed according to Calvert's calculation [9].

The overall response rate was 78% (39/50) with a complete response rate of 62% (Table 5). The response rate tended to be higher in women with residual disease ≤1 cm than in those with more residual disease, but the difference was not significant (χ^2_1 complete/partial versus no change/progression). No marked difference emerged in response rate between strata of low and high paclitaxel doses.

Table 4. Doses of paclitaxel actually given and doses planned

Paclitaxel dose planned (mg/m^2)	Dose actually given (mg/m^2) Mean	(S.D.; range)
I (150 mg/m^2)	150	—
II (175 mg/m^2)	175	—
III (200 mg/m^2)	200	—
IV (225 mg/m^2)	215	(7.2; 204—225)
V (250 mg/m^2)	243	(5.7; 238—250)

*One patient stopped at the 4th course because of grade 3 neurotoxicity. See the text for reasons for dose reduction in the IV and V dose level. The patients who stopped treatment on account of progressive disease are considered for the cycles actually given.

Table 5. Response after six cycles of treatment

	Response			
	Complete response *n* (%)	Partial response *n* (%)	No change *n* (%)	Progressive disease *n* (%)
Total ($n = 50$)	31 (62)	8 (16)	5 (10)	6 (12)
Residual tumour (cm)				
≤ 1 ($n = 14$)	10 (71)	2 (14)	1 (7)	1 (7)
>1 ($n = 36$)	21 (58)	6 (17)	4 (11)	5 (14)
Paclitaxel dose*				
Low doses ($n = 15$)	11 (73)	2 (13)	—	2 (13)
High doses ($n = 35$)	20 (57)	6 (17)	5 (14)	4 (11)

*Low doses ≤ 200 mg/m^2 paclitaxel and 300 mg/m^2 carboplatin. High doses ≥ 225 mg/m^2 paclitaxel and 300 mg/m^2 carboplatin.

DISCUSSION

The results of this phase I-II trial suggest that carboplatin and paclitaxel can be administered safely to patients with advanced ovarian carcinoma.

The maximum dose given was 250 mg paclitaxel and 300 mg carboplatin. We did not reach the MTD as defined by the protocol, but at the dose of 250 mg/m^2 paclitaxel plus 300 mg/m^2 carboplatin, the frequency of peripheral neuropathy requiring dose reduction was approximately 67% (4/6 patients). Thus, from a clinical point of view the maximum dose that we considered safe was 225 mg paclitaxel and 300 mg carboplatin.

Haematological toxicity has been reported as dose limiting in phase I-II strata of paclitaxel alone [1, 2]. In this study, haematological toxicity was not marked. Although neutropenia was observed during most courses, even at low paclitaxel doses, it did not last long and in no case was G(M)-CSF support given. Paclitaxel was administered after carboplatin and no important haematological toxicity was observed. However, no data are available on the role of sequence with carboplatin plus paclitaxel [10]. These results are of particular interest. In fact, carboplatin causes more bone marrow toxicity (leucopenia and thrombocytopenia) than cisplatin [11], which has been more frequently tested in previous studies in association with taxol [1–3, 10]. High-grade alopecia was observed at all doses, but other toxicities were not dose limiting.

These results are generally consistent with the few published data on the same issue. One study found that paclitaxel alone could be safely administered up to 250 mg/m^2 every 3 weeks with G(M)-CSF support, but that trial included previously treated patients [12]. Peripheral neuropathy was not reported in 9 women with previously untreated ovarian cancer who received 135 mg/m^2 paclitaxel and escalating doses of carboplatin ranging from an AUC of 5 to 10 [4].

The importance of high-dose chemotherapy has been shown for ovarian cancer. For example, cisplatin doses have been directly related to response rate and survival [13, 14]. No clear data are available on the role of paclitaxel dose intensity in the treatment of ovarian cancer. A European–Canadian trial did not show any improvement in the response rate with a paclitaxel dose of 175 mg/m^2 in comparison with lower doses (although the progression-free survival was slightly longer in the high-dose group) [15]. A small trial of paclitaxel dose intensification conducted in the U.S. on 15 ovarian cancer patients showed that raising the dose from 45 mg/m^2/week to 83 mg/m^2/week was associated with an enhanced rate of disease response [16].

Finally, in the present study, the overall response rate was 78% (39/50), with a complete response rate of 62% (31/50). Thus, most of the responders obtained a complete response. There was no marked difference in the response rate in strata of dose levels of paclitaxel. However, the main end point of the trial was not to assess response, and the finding should be considered cautiously because of the small number of women treated. The response rate is higher than previously reported, but our population comprised untreated women. Further, the response was higher in women with residual tumour ≤ 1 cm. This is consistent with the recognised better effect of chemotherapy in ovarian cancer cases with minimal residual disease [17].

1. Rowinsky EK, Onetto N, Canetta R, *et al.* Taxol: the first of the takanes, an important new class of antitumor agents. *Semin Oncol* 1992, **19**, 646–662.
2. McGuire WP. Taxol: a new drug with significant activity as salvage therapy in advanced epithelial ovarian carcinoma. *Gynecol Oncol* 1993, **51**, 78–85.
3. McGuire WP, Hoskins WJ, Brady MF, *et al.* Taxol and cisplatin (TP) improves outcomes in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP). *Proc Am Soc Clin Oncol* 1995, **14**, 771 (abstract).
4. Ozols RF, Kilpatrick D, O'Dwyer P, *et al.* Phase I and pharmacokinetic study of taxol (T) and carboplatin (C) in previously untreated patients (PTS) with advanced epithelial ovarian cancer (OC): a pilot study of the gynecologic oncology group. *Proc Am Soc Clin Oncol* 1993, **12**, 824 (abstract).
5. Ten Bokkel Huinink WW, Veenhof CHN, *et al.* Carboplatin and paclitaxel (taxol) in patients with advanced ovarian cancer, a dose-finding study. *Proc ESMO* 1994, **495**, 99 (abstract).
6. Bissett D, Kaye SB. Taxol and taxotere—current status and future prospects. *Eur J Cancer* 1993, **29A**, 1228–1231.
7. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel–Haenszel procedure. *J Am Stat Assoc* 1963, **58**, 690–700.
8. Bolis G. Pilot study with fixed-dose carboplatin and escalating paclitaxel in advanced ovarian cancer. *Semin Oncol* 1995, **22**, 32–36.
9. Calvert AH, Newell DR, Gumbrell LA, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989, **7**, 1748–1756.
10. Rowinsky EK, Gilbert MR, McGuire WP, *et al.* Sequences of taxol and cisplatin: a phase I and pharmacologic study. *J Clin Oncol* 1991, **9**, 1692–1703.
11. Mangioni C, Bolis G, Pecorelli S, *et al.* Randomized trial in advanced ovarian cancer comparing cisplatin and carboplatin. *J Natl Cancer Inst* 1989, **81**, 1464–1471.
12. Sarosy G, Kohn E, Stone DA, *et al.* Phase I study of taxol and G-CSF in patients with refractory ovarian cancer. *J Clin Oncol* 1992, **10**, 1165–1170.
13. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol* 1987, **5**, 756–757.
14. Levin L, Hryniuk W. The application of dose intensity to problems in chemotherapy of ovarian and endometrial cancer. *Semin Oncol* 1987, **14**(Suppl. 4), 12–19.
15. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, *et al.* European–Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol* 1994, **12**, 2654–2666.
16. Sarosy G, Kohn E, Link C, *et al.* Taxol dose intensification (D.I.) in patients with recurrent ovarian cancer. *Proc Am Soc Clin Oncol* 1992, **11**, 716 (abstract).
17. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL, *et al.* Long-term survival in ovarian cancer. *Eur J Cancer* 1991, **27**, 1367–1372.

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