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ORIGINAL ARTICLE

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A multicenter phase II study of cisplatin and docetaxel (Taxotere) in the first-line treatment of advanced ovarian cancer: a GINECO study

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Abstract *Purpose*: A multicenter phase II study to evaluate the antitumor effect and safety of docetaxel in combination with cisplatin as first-line chemotherapy for advanced ovarian cancer. *Methods*: Enrolled in the study were 45 patients who were to receive six courses of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 every 21 days with hydration and steroid prophylaxis after initial debulking surgery. Imaging techniques and radiography were used to assess clinical tumor response, and second-look surgery was required for patients with complete clinical responses and for those without clinically measurable disease. *Results*: The overall clinical response rate in 29 patients with clinically measurable disease was 58% (41% complete response). A complete pathologic response was seen in 9 of 34 patients who underwent second-look laparotomy, while microscopic disease was found in 10 patients. The median time to progression was 14.4 months (95% CI 8.4–20.4 months), with a median overall survival of 43 months (95% CI 21.1–65.0 months). Patients received a median number of six cycles at a dose intensity of 98%. Grade 3–4 neutropenia was seen in 80% of patients, but was manageable. No patients withdrew because of fluid retention. *Conclusions*: The combination of docetaxel with cisplatin confers high clinical and pathologically verified tumor response rates and is well tolerated in the first-line management of advanced ovarian cancer.

Keywords Docetaxel · Cisplatin · Ovarian cancer · Taxanes · Treatment

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Introduction

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies and is the fifth most frequent cause of cancer death in patients [22]. Early (stage I) disease is curable with surgery in a high percentage of patients, but ovarian cancer is often asymptomatic until advanced, and most patients present with widespread disease. Indeed, approximately 75% of patients are at FIGO (International Federation of Gynecology and Obstetrics) stages III–IV at the time of diagnosis [17]. Five-year survival rates fall progressively with more advanced ovarian cancer, to around only 11% in patients with stage IV malignancies [20].

Platinum-based chemotherapy has been the mainstay of treatment for advanced epithelial ovarian cancer since the activity of regimens based on cisplatin was demonstrated in the early 1980s [5, 16], with combinations of a platinum drug with an alkylating agent being broadly accepted as standard therapy

thereafter. In general, higher clinical response rates and longer progression-free intervals are achieved with platinum-based combination therapy than with alkylating agents alone or with non-platinum regimens [1]. Long-term disease control with cisplatin and cyclophosphamide (with doxorubicin) is seen in fewer than 10% of patients with incompletely resected stage III ovarian cancer, and in fewer than 5% of those with stage IV disease [29].

Further progress was made at the end of the 1980s when the activity of the taxane paclitaxel was demonstrated in patients with ovarian cancer resistant to platinum therapy [18]; this was confirmed in a further trial in patients with less heavily pretreated disease who received a higher starting dose of paclitaxel [30]. These observations, together with the demonstration of acceptable tolerability of paclitaxel plus cisplatin [28], led to two phase III trials in a total of more than 1000 patients: the Gynecologic Oncology Group's GOG 111 study [19] and the Intergroup Trials OV10 trial [27]. Both investigations showed higher tumor response rates and significantly longer median progression-free and overall survival in patients receiving paclitaxel plus cisplatin than in those receiving cyclophosphamide plus cisplatin. Paclitaxel/platinum combinations are therefore now replacing platinum/alkylating agent regimens in the first-line therapy of advanced ovarian cancer [13].

Docetaxel is a recently introduced semisynthetic taxoid that has shown activity in a range of different tumor types. Like paclitaxel, docetaxel is a spindle poison that arrests cell division through effects on microtubule assembly, but the drug is 1.2–2.6 times more cytotoxic than paclitaxel and over 1000 times more cytotoxic than cisplatin or etoposide in ovarian cancer cell lines [7, 15]. Furthermore, docetaxel has shown activity in vitro and in the clinical setting in tumors resistant to paclitaxel [10, 34], and has shown synergy with platinum agents in ovarian cancer cells in vitro, together with good activity in cell lines resistant to these drugs [15].

Very encouraging activity of docetaxel was found in four phase II studies in which a dose of 100 mg/m^2 was given every 3 weeks to a total of 340 patients with platinum-refractory advanced ovarian cancer [2, 8, 12, 25]. Overall tumor response rates of 26–40% were demonstrated, with pooled data showing 14 complete and 79 partial responses for an overall response rate of 30% [14]. Median overall survival ranged from 8 to 10.4 months.

These findings, together with the known neurotoxicity of both paclitaxel and cisplatin, have prompted interest in the potential of docetaxel as an alternative to paclitaxel as a platinum partner for first-line therapy in advanced ovarian cancer. The present open-label multicenter study was therefore carried out as a phase II investigation of the tolerability and efficacy of docetaxel plus cisplatin, both given at a dosage of 75 mg/m^2 every 21 days, in this patient population.

Patients and methods

Study patient sample and objectives

Patients aged between 18 and 70 years were required to have histologically confirmed FIGO stage III or IV epithelial ovarian cancer, with macroscopic evidence of residual disease after initial debulking surgery, and cytologic confirmation of any stage IV classification that was based on pleural effusion. Patients with borderline or non-epithelial tumors were not included. Study enrolment was required within 6 weeks of initial surgery, and participants were required to have a performance status (WHO scale) of 0–2 (i.e. from normal activity levels to requirement for bed rest for up to 50% of each day) and a life expectancy of at least 12 weeks. Normal bone marrow and renal function were required as shown by a neutrophil count of at least 2000 cells/mm^3, platelet count of at least 100,000/mm^3, and serum creatinine level of less than 120 μmol/l. Adequate hepatic function was indicated by serum bilirubin levels of less than 1.25 times the upper limit of the normal range (ULN), serum aspartate transaminase (AST) and alanine aminotransferase (ALT) levels up to 1.5 times ULN, and alkaline phosphatase levels below 2.5 times ULN.

Major grounds for exclusion included a history of previous antitumor chemo- or radiotherapy, presence of cerebral metastases, history of any other malignancy with the exception of cervical cancer in situ or basal cell cancer, peripheral neuropathy, and cardiac arrhythmia or history of myocardial infarction, atrioventricular block, angina pectoris or cardiac insufficiency.

Before entry into the study, patients underwent a baseline assessment that included a full physical examination and neurologic assessment, hematologic and biochemical assessment, electrocardiographic examination (ECG), and determination of CA125 levels. Full blood and platelet counts were carried out at least once weekly during treatment, with clinical and biologic examinations (including CA125 analysis). Clinical tumor assessments were carried out by radiologic examination of the thorax, and by postoperative abdominal and pelvic ultrasound or computed tomography scan. Tumor response was assessed according to WHO criteria. The primary objective of the study was the assessment of objective tumor response after up to six cycles of chemotherapy. Secondary endpoints were tolerability, duration of tumor response, time to progression of disease and overall survival. The study was carried out in accordance with the Declaration of Helsinki and its revisions (Tokyo, Venice and Hong Kong), and the study protocol was approved by the participating centers and the French Bio-Ethics Committee 'Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale' at the Hotel-Dieu Hospital, Paris. Written and informed consent was obtained from each patient before enrolment.

Study treatments

On day 1, docetaxel was given by intravenous infusion over 1 h at an initial dose of 75 mg/m^2, followed by hydration with 1000 ml normal saline. Cisplatin 75 mg/m^2 was administered intravenously over 30 min, 0.5–1 h after docetaxel, with subsequent hydration with 3000 ml normal saline. Study treatment was repeated every 21 days for a total of six courses or until disease progression. Patients received prophylactic oral prednisolone at a dosage of 50 mg twice daily for 5 days, with the first dose being given 12 h before the start of each cycle of docetaxel. Antiemetic therapy was given as required and scalp cooling was administered to limit alopecia. Two-step dose reductions were allowed for docetaxel and/or cisplatin (depending on circumstances as detailed below), first to 60 mg/m^2 and finally to 50 mg/m^2 (for both drugs). No antibiotics and no recombinant colony stimulating factors were given prophylactically during the course of this investigation.

Docetaxel dose reduction was required for patients with febrile neutropenia, defined as a neutrophil count $< 500/mm^3$ with single temperature reading $> 38.5°C$ or three separate readings of 38°C over 24 h.

Dose delay for up to 2 weeks was stipulated for neutrophil counts below $1500/mm^3$ and/or platelet counts below $100{,}000/mm^3$, with subsequent dose reduction as required according to nadir count and recovery time. Dose reductions were stipulated for peripheral neuropathy of grade 2 severity (docetaxel and cisplatin); for AST or ALT values 1.5–3.5 times ULN or alkaline phosphatase values 2.5–6 times ULN (docetaxel); and for renal toxicity shown by a serum creatinine reading of 120–150 μmol/l after hydration (cisplatin). Neuropathic, hepatic or renal toxicities of severities greater than these necessitated withdrawal from the study. Patients were also required to withdraw from the study if reductions in the dose of the same drug were required on more than two occasions, or if it was necessary to delay a chemotherapy cycle by more than 2 weeks. Dose reductions were also required for patients with mucositis of severity grade 2 or worse, or with grade 3 diarrhea that did not respond to treatment with loperamide.

Dose delay (until attainment of grade 1 severity or less) and subsequent dose reduction were specified for patients with grade 3 cutaneous reactions. Continuation of study treatment in patients who developed fluid retention was at the discretion of the investigator. Withdrawal of docetaxel was specified for severe hypersensitivity reactions (e.g. bronchospasm, generalized urticaria, angioedema, severe hypotension), with therapy to be started again within 24 h of resolution of symptoms (after treatment with agents such as epinephrine and bronchodilators). In the event of a second severe reaction, the patient was required to withdraw from the study.

Tumor and toxicity assessments

Clinical responses were assessed in patients with clinically measurable or evaluable disease. Measurable disease was defined as the presence of at least one lesion whose largest diameter was 32 cm. Clinical disease was assessed by clinical and CT scan evaluation prior to chemotherapy, and after the third and sixth cycle. CA125 levels were assessed during each cycle.

Complete clinical responses were denoted by the absence of all measurable and evaluable lesions for at least 4 weeks after the end of study treatment, with normal levels of CA125. A partial clinical response was defined as a reduction of at least 50% in the sum of the perpendicular diameters of all clinically measurable lesions, with no progression or appearance of new lesions, for at least 4 weeks.

Reassessment 'second-look' laparotomy was required by protocol for patients with no clinical evidence of disease at the end of therapy. Patients were classified according to pathologic response into one of the following categories:

- Complete surgical (pathologic) tumor response, defined as the absence of any abdominal lesion with negative biopsies, together with the absence of any extraabdominal disease.
- Partial response, defined as a reduction of at least 50% in the sum of all residual masses or persistence of microscopic disease only with no progression or appearance of any new lesion.
- Persistent disease, if macroscopic residual lesions (≤ 2 cm) present.

Stable disease was defined as a reduction of less than 50% or increase of less than 25% in the sum of the perpendicular diameters of all measurable lesions, without appearance of new lesions. Disease progression was defined as an increase of at least 25% in the sum of the perpendicular diameters of all measurable lesions or the appearance of new lesions. Progression-free survival was measured from the date of study registration to first clinical progression or last contact, and overall survival was measured from the date of study registration to the date of death.

Adverse events were graded according to National Cancer Institute Common Toxicity Criteria [23], with the worst grading for each toxicity being recorded for each course of chemotherapy.

Statistical considerations

The number of patients required for this phase II study was determined for an expected complete pathologic response rate of 30%. To obtain a complete pathologic response rate of 30% with a precision of $+14\%$ using a 95% CI determined by normal approximation, 41 evaluable patients needed to be included in the study, assuming an α error rate of 0.05. Considering that approximately 10% of patients would be non-evaluable, a maximum of 45 patients were required to be enrolled in the study.

The intent to treat (ITT) population comprised all enrolled patients. All patients included in the study were assessed for safety. Statistical analysis was descriptive. Quantitative parameters were summarized by mean, standard deviation, median, minimum and maximum and qualitative parameters by frequencies and percentages. Confidence intervals were provided for pathologic response rates. Overall survival, time to progression, duration of response, and progression-free survival were calculated for the ITT population using the Kaplan-Meier method.

Results

Patient characteristics

From March to November 1997, 45 patients with a median age of 56 years (range 39–69 years) were enrolled in the study. One patient was subsequently found to be ineligible (no residual disease after debul-

Table 1 Patient characteristics

No. of patients enrolled	45	
No. of patients eligible	44	
Age (years)		
Median	56	
Range	39–69	
WHO performance status (*n*, %)		
0	13	29
1	24	53
2	8	18
Tumor histology (*n*, %)		
Serous	36	79
Endometrioid	4	9
Other	5	12
Tumor grade (*n*, %)		
1	9	19
2	16	35
3	7	16
Unknown	13	30
FIGO stage (*n*, %)		
III	32	71
IV	13	29
Residual tumor size (*n*, %)		
< 2 cm	14	29
≥ 2 cm	31	71
Ascites present (%)		
Yes		22
No		78

Table 2 Dose delivery (259 cycles of treatment were administered in total)

	No. of courses (%)	Reason	No. of courses
Dose delay ≥7 days	14 (5)	Infection	1
		Neutropenia	4
		Asthenia	1
		Other	8
Dose reduction			
Docetaxel	6 (2)	Infection	2
		Nausea/vomiting	1
		Neuropathy	1
		Mucositis	1
		Diarrhea	1
Cisplatin	7 (3)	Infection	1
		Nausea/vomiting	1
		Neuropathy	1
		Diarrhea	2
		Raised serum creatinine level	2

king surgery). The characteristics of the enrolled patients are summarized in Table 1. The predominant histologic tumor type was serous adenocarcinoma (79% of patients). Most patients (71%) had FIGO stage III disease, and 29% had stage IV. After surgery, 71% had residual lesions at least 2 cm in diameter.

Treatment delay and dose modification

In total, 259 cycles of treatment were administered, with a median of six cycles per patient (range three to nine). Dose reductions were required in six cycles (2%; six patients) for docetaxel and in seven cycles (3%; six patients) for cisplatin. A total of 14 cycles (5%) were delayed (Table 2), 6 because of toxicity and 8 for other reasons (constipation 1, surgery 1, chest pain check-up 1, personal convenience 4, and unknown reason 1). The median dose intensity was 98% (95% CI 64–98%) for both drugs. Treatment was discontinued at study completion in 42 patients including one ineligible patient, and because of disease progression in three patients.

Response to treatment

Tumor response was assessed by physical examination and CT scan in 29 patients with clinically measurable disease (Table 3). The overall response rate was 58%, with complete response being noted in 12 patients (41%). The overall clinical response rate for the ITT population of 45 patients was 38% (95% CI 24–52%). All 28 patients who had no detectable clinical disease at the end of six cycles underwent second-look laparotomy as required by protocol. The procedure was also performed in seven additional patients whose clinically detectable disease did not progress during treatment. Of the 34 patients so treated, 9 showed a complete pathologic response (i.e. no histologic evidence of disease); microscopic disease was noted in 10 patients, and persistent disease in a further 15 (Table 4). Up to three additional study treatment cycles were given after reassessment surgery in seven patients with residual disease, including three patients with microscopic disease.

Table 4 Reassessment (second-look) laparotomy findings

Result	No. of patients	Percentage of patients
Complete pathologic response	9	20
Microscopically positive	10	22
Persistent disease	15	34
<2 cm	7	16
≥2 cm	8	18
Procedure contraindicated or refused	10	22
Ineligible	1	2
Total	45	100

The median time to progression was 14.4 months (95% CI 8.4–20.4 months; Fig. 1). As of November

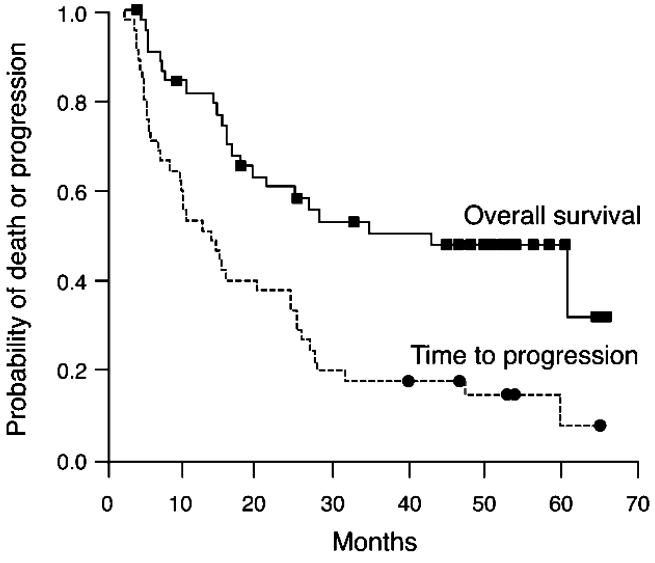

Fig. 1 Time to progression and overall survival of patients with advanced ovarian cancer treated with docetaxel–cisplatin

Table 3 Clinical responses. Percentages do not add up to 100 because of rounding

No. of evaluable patients[a]	Complete response (%)	Partial response (%)	Overall response rate (%)	Stable disease (%)	Disease progression (%)
29	12 (41)	5 (17)	17 (58)	2 (7)	10 (34)

[a]Patients with measurable disease

Table 5 Hematologic toxicities (NCI Common Toxicity Criteria)

Toxicity	Percentage of cycles		Percentage of patients	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Leukopenia	59	11	64	30
Neutropenia	28	46	14	82
Anemia	69	5	82	16
Thrombocytopenia	2	0	5	0
Febrile neutropenia	0	1	0	2
Infection	3	3	13	16

Table 6 Non-hematologic toxicities

Toxicity	Percentage of patients	
	Grade 2	Grade 3–4
Alopecia	79	0
Nausea/vomiting	30	19
Hypersensitivity reactions	2	0
Diarrhea	5	5
Elevated creatinine level	5	0
Neuropathy	5	0
Cutaneous reactions	7	0
Peripheral edema	7	5
Pulmonary edema	0	2
Myalgia/arthralgia	5	0

2002, after a median follow-up time of 53 months, 22 patients were alive and 23 had died. The median overall survival duration was 43 months (95% CI 21.1–65.0 months; Fig. 1).

Toxicity

Toxicity was evaluable for 240 treatment cycles (Table 5). As expected, neutropenia was the main adverse event, and was noted in 80% of patients (38% grade 3 and 42% grade 4) and 46% of treatment courses (31% grade 3 and 15% grade 4). Three cases of grade 3–4 infection and only one case of febrile neutropenia were reported by cycle. Grade 3–4 anemia was observed in 16% of patients and 5% of cycles, with transfusion being required in eight cycles (3%). Grade 1–2 thrombocytopenia was seen in only 5% of patients and 2% of cycles. No grade 3 or 4 thrombocytopenia was observed. Grade 3 peripheral edema (symptomatic limiting function or severe edema or anasarca) was observed in two patients after treatment completion (i.e. after six treatment courses), but there were no reports of pericardial or pleural effusion (non-hematologic adverse events are listed in Table 6). No patients withdrew because of fluid retention. Hypersensitivity reactions, limited to grade 2 only, were noted in four patients. Neuropathy occurred in 12 patients, 10 grade 1 and 2 grade 2. One patient developed acute pulmonary edema and renal insufficiency leading to death during the sixth cycle of therapy. The acute renal insufficiency occurred 7 days after administration of chemotherapy and was related to the administration of cisplatin and a concurrent urinary infection. Suspected pulmonary embolism was not confirmed.

Discussion

Docetaxel is a logical choice for combination with a platinum agent because of its improved therapeutic index relative to paclitaxel as suggested by preclinical studies [3], in addition to the nonoverlapping toxicity profiles of docetaxel and the platinums. Most notably, docetaxel is associated with only minimal neurotoxicity, unlike paclitaxel, and mild neuropathic symptoms only were accordingly seen in the present study. Docetaxel also offers a substantial practical advantage over paclitaxel because the 1-h infusion as used in the present trial has been identified as the optimum means of delivering docetaxel [4]. This contrasts sharply with the 3- or 24-h infusion times required for paclitaxel. Furthermore, 1-h docetaxel infusion allows the use of scalp cooling to limit the development of alopecia.

The activity of docetaxel as second-line monotherapy has already been clearly demonstrated in patients with platinum-refractory ovarian carcinoma, with an overall tumor response rate of up to 40% [2, 8, 12, 25]. Neutropenia and fluid retention were the only limiting toxicities in these trials; however, none included steroid prophylaxis, which is now known to reduce the incidence and severity of fluid retention [26] and was incorporated into this study (as with other docetaxel trials carried out since the mid-1990s). Indeed, grade 3 peripheral edema was noted in two patients only in the present study, and no patients withdrew because of this adverse event. Neutropenia was the main toxicity of docetaxel in the phase I and II monotherapy trials, but did not appear to be dose- or schedule-dependent [4]. In light of these observations, the 80% rate by patient and 46% by cycle of grade 3–4 neutropenia found in the present study was not unexpected. Nevertheless, neutropenia did not cause any treatment withdrawal and was readily managed. It is also noteworthy that only two episodes of febrile neutropenia were reported. This compares favorably with the data from paclitaxel and cisplatin studies in which grade 3–4 neutropenia was reported (64% of cycles by Piccart et al. [27], with 2% febrile neutropenia; and in 92% of patients by McGuire et al. [19]).

First-line 3-weekly cisplatin-based dual therapy incorporating paclitaxel has been studied extensively since 1996 in a number of major trials: GOG 111 [19] and OV10 [27] which showed overall clinical response rates of 73% and 58.6%, respectively, with overall median survivals of 38 and 35.6 months. Similarly, comparisons of cisplatin- and carboplatin-based paclitaxel-containing regimens showed overall response rates

of 62% [24] and 80% [6], with overall median survival of 30 months, in the cisplatin-paclitaxel arms. Cisplatin at a dose of 75 mg/m^2 was scheduled in all these trials. However, these promising responses to treatment were accompanied by concerns over toxicity, particularly with respect to neurosensory and neuromotor effects. In addition, two recently published randomized trials (ICON Group 2002), and the GOG 132 study of 3-weekly paclitaxel 135 mg/m^2 over 24 h plus cisplatin 75 mg/m^2 compared with high-dose cisplatin (100 mg/m^2) or paclitaxel (200 mg/m^2 over 24 h) alone [21], did not show any difference in overall survival between paclitaxel plus carboplatin and control or between cisplatin and paclitaxel.

The interest in maximizing clinical benefit of taxane/platinum therapy while minimizing chemotherapy-related adverse effects has prompted investigations of docetaxel plus cisplatin by two other groups in addition to ours. Both these phase II studies involved the same regimen as specified by our protocol (both drugs given as 75 mg/m^2 every 3 weeks for six cycles) with routine steroid premedication. The Scottish Gynaecological Cancer Trials (SGCT) Group reported an overall clinical response rate of 69% (complete response rate 38%) in 39 evaluable patients [33], although it should be noted that this study has also incorporated a cohort of patients who received docetaxel 85 mg/m^2 and recruited patients with disease stages Ic to IV. Interim data from the Russian RAMS study showed a clinical response rate of 73.6% in 38 evaluable patients [9]; a complete clinical response has been reported in 42.1%, although this has been pathologically verified in only four patients.

In accordance with the above findings, our results show an encouraging overall clinical response rate of 58% in 29 patients with clinically evaluable lesions, with a complete response rate of 41%. In particular, a high proportion of our patients (100% of the 35 non-progressive patients) underwent a second-look laparotomy, which showed a pathologically verified complete tumor response rate of 20%, with a microscopic residual disease rate of 22%. These results were accompanied by median overall and progression-free survival times of 43 (95% CI 21.1–65.0 months) and 14.4 months (95% CI 8.4–20.4 months), respectively, which are comparable to survival times reported with paclitaxel and cisplatin combinations. Neuropathic symptoms did not exceed grade 2 severity in the present study. This mild neurotoxicity is concordant with available results from the two other phase II studies of docetaxel and cisplatin [19, 27], but is less severe than the neurotoxicity seen with the paclitaxel–cisplatin combination: grade 3–4 neurosensory toxicity was reported in 14% of cycles by Piccart et al. [27] and in 4% of patients by McGuire et al. [19]. The manageable myelotoxicity experienced by our patients is also comparable to observations in these other trials in which patients received docetaxel 75 mg/m^2. The acceptable safety of docetaxel and cisplatin observed in the present trial is underlined further by the achievement of dose intensities of 98% for both drugs.

Current interest in the replacement of cisplatin by carboplatin in taxane combinations as first-line therapy in ovarian carcinoma has culminated in a phase III trial comparing docetaxel/carboplatin with paclitaxel/carboplatin in 1077 patients [31, 32]. Both regimens conferred clinical/radiologic response rates of over 60%, but the paclitaxel-based regimen was associated with more sensory neuropathy (grade 2/3 30% vs 11%; $P < 0.01$) during therapy and continuing out to at least 14 months from randomization, while docetaxel-based treatment showed a higher incidence of grade 4 neutropenia (80% vs 55%; $P < 0.01$). However, as in our study and others in which docetaxel was used, myelotoxicity was predictable and readily managed. Recent data from the International Collaborative Ovarian Neoplasm (ICON) Group reinforce the opinion that carboplatin is likely to be the platinum agent of choice in the future [11], and it is to be anticipated that research will continue to optimize chemotherapy for advanced ovarian cancer.

Thus, the clinical and pathologic response rates, median survivals, and toxicity profiles observed with docetaxel plus cisplatin, particularly when viewed in the context of similar studies with this type of combination, highlight docetaxel as an active and well-tolerated platinum partner for the first-line management of advanced epithelial ovarian cancer.

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