

# Phase III Randomized Trial of Docetaxel–Carboplatin Versus Paclitaxel–Carboplatin as First-line Chemotherapy for Ovarian Carcinoma

Paul A. Vasey, Gordon C. Jayson, Alan Gordon, Hani Gabra, Rob Coleman, Ronnie Atkinson, David Parkin, James Paul, Andrea Hay, Stan B. Kaye

On behalf of the Scottish Gynaecological Cancer Trials Group

**Background:** Chemotherapy with a platinum agent and a taxane (paclitaxel) is considered the standard of care for treatment of ovarian carcinoma. We compared the combination of docetaxel–carboplatin with the combination of paclitaxel–carboplatin as first-line chemotherapy for stage Ic–IV epithelial ovarian or primary peritoneal cancer. **Methods:** We randomly assigned 1077 patients to receive docetaxel at 75 mg/m<sup>2</sup> of body surface area (1-hour intravenous infusion) or paclitaxel at 175 mg/m<sup>2</sup> (3-hour intravenous infusion). Both treatments then were followed by carboplatin to an area under the plasma concentration–time curve of 5. The treatments were repeated every 3 weeks for six cycles; in responding patients, an additional three cycles of single-agent carboplatin was permitted. Survival curves were calculated by the Kaplan–Meier method, and hazard ratios were estimated with the Cox proportional hazards model. All statistical tests were two-sided. **Results:** After a median follow-up of 23 months, both groups had similar progression-free survival (medians of 15.0 months for docetaxel–carboplatin and 14.8 months for paclitaxel–carboplatin; hazard ratio [HR] docetaxel–paclitaxel = 0.97, 95% confidence interval [CI] = 0.83 to 1.13; *P* = .707), overall survival rates at 2 years (64.2% and 68.9%, respectively; HR = 1.13, 95% CI = 0.92 to 1.39; *P* = .238), and objective tumor (58.7% and 59.5%, respectively; difference between docetaxel and paclitaxel = –0.8%, 95% CI = –8.6% to 7.1%; *P* = .868) and CA-125 (75.8% and 76.8%, respectively; difference docetaxel–paclitaxel = –1.0%, 95% CI = –7.2% to 5.1%; *P* = .794) response rates. However, docetaxel–carboplatin was associated with substantially less overall and grade 2 or higher neurotoxicity than paclitaxel–carboplatin (grade ≥2 neurosensory toxicity in 11% versus 30%, difference = 19%, 95% CI = 15% to 24%; *P* < .001; grade ≥2 neuromotor toxicity in 3% versus 7%, difference = 4%, 95% CI = 1% to 7%; *P* < .001). Treatment with docetaxel–carboplatin was associated with statistically significantly more grade 3–4 neutropenia (94% versus 84%, difference = 11%, 95% CI = 7% to 14%; *P* < .001) and neutropenic complications than treatment with paclitaxel–carboplatin, although myelosuppression did not influence dose delivery or patient safety. Global quality of life was similar in both arms, but substantive differences in many symptom scores favored docetaxel. **Conclusions:** Docetaxel–carboplatin appears to be similar to paclitaxel–carboplatin in terms of progression-free survival and response, although longer follow-up is required for a definitive statement on survival. Thus, docetaxel–carbopla-

tin represents an alternative first-line chemotherapy regimen for patients with newly diagnosed ovarian cancer. [J Natl Cancer Inst 2004;96:1682–91]

Platinum-based chemotherapy remains the cornerstone of treatment for ovarian carcinoma, and over the last 20 years surgical cytoreduction plus chemotherapy has improved the 5-year survival in the United States (1). Furthermore, after publication of the results of a number of pivotal trials in the 1990s, chemotherapy with a platinum agent and a taxane (paclitaxel) is now considered the standard of care (2–6).

However, in metastatic breast cancer, docetaxel, a semisynthetic taxane with pharmacologic and pharmacokinetic advantages over paclitaxel (7–10), has shown superiority over anthracyclines and paclitaxel in randomized trials (11,12). Docetaxel has also been evaluated in ovarian cancer. Phase II trials have indicated a level of efficacy comparable to that of paclitaxel (13), and, in paclitaxel-resistant patients, docetaxel retains an important degree of clinical activity (14). The feasibility of a docetaxel–carboplatin combination treatment for ovarian cancer was confirmed in a large feasibility study (15), and the recommended three-weekly dose was docetaxel at 75 mg/m<sup>2</sup> of body surface area and carboplatin to an area under the plasma concentration–time curve (AUC) of 5. Independent results from the United States showed a high clinical response rate and good tolerability for docetaxel at 60 mg/m<sup>2</sup> plus carboplatin to an AUC of 6 when administered every 3 weeks (16).

In light of these promising findings, a randomized phase III study, SCOTROC (Scottish Randomised Trial in Ovarian Cancer) 1, was begun to compare efficacy, tolerability, and quality of life outcomes of docetaxel–carboplatin with paclitaxel–carboplatin as initial chemotherapy for stage Ic–IV ovarian and/or peritoneal cancers.

*Affiliations of authors:* Cancer Research U.K. Department of Medical Oncology, Glasgow, U.K. (PAV, JP, AH); Christie Hospital, Manchester, U.K. (GCJ); Sammons Cancer Center, Dallas, TX (AG); Hammermith Hospital, London, U.K. (HG); Weston Park Hospital, Sheffield, U.K. (RC); Belfast City Hospital, Northern Ireland, U.K. (RA); Aberdeen Royal Infirmary, Aberdeen, U.K. (DP); Royal Marsden Hospital, London, U.K. (SBK).

*Correspondence to:* Paul A. Vasey, MD, Division of Oncology, Joyce Tweddell Bldg., Royal Brisbane and Women's Hospital, Herston, Queensland 4029, Australia (e-mail: paul\_vasey@health.qld.gov.au).

See “Notes” following “References.”

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## PATIENTS AND METHODS

### Patients

Between October 8, 1998, and May 8, 2000, 1077 patients from 83 international centers were randomly assigned to treatment with docetaxel-carboplatin (n = 539) or with paclitaxel-carboplatin (n = 538). The two treatment arms were well matched with respect to demographic and disease characteristics (Table 1). The patients' progress through the trial is shown in Fig. 1.

Inclusion criteria were women 18 years of age or older with histologically confirmed epithelial ovarian carcinoma or ovarian-type peritoneal carcinomatosis, an International Federation of Gynecologic Oncology (FIGO) stage of Ic-IV, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, no prior chemotherapy or radiotherapy, and adequate levels of bone marrow, hepatic, and renal function. Exclusion criteria included mixed mesodermal tumors, borderline tumors, tumors termed "possibly malignant," concurrent malignancies, malignancy within the previous 5 years (except curatively treated carcinoma *in situ* of the cervix or basal cell carcinoma), prior serious allergic reactions, pregnancy, lactation, or peripheral neuropathy of grade 2 or higher.

The study had full multicenter ethics committee approval, and all patients gave written informed consent. Randomization took place within 6 weeks of surgery, and patients were allocated to treatment by a minimization algorithm that used the following criteria: extent of residual disease, center, FIGO stage, performance status, tumor grade, interval debulking intention, CA-125 level available before treatment, and presence or absence of primary peritoneal cancer.

**Table 1.** Characteristics of patients in the Scottish Randomised Trial in Ovarian Cancer 1\*

Characteristic	Docetaxel-carboplatin arm (n = 539)	Paclitaxel-carboplatin arm (n = 538)
Median age y (range)	59 (21-85)	59 (19-84)
FIGO stage, %		
Ic-II	19	20
III-IV	81	80
ECOG performance status, %		
0 or 1	87	87
2	13	13
Postoperative residuum, %		
0 or microscopic	33	33
≤2 cm	30	30
>2 cm	37	37
Primary peritoneal cancer, %	8	9
Cell type, %		
Serous papillary	44	44
Mucinous	4	2
Clear cell	5	4
Endometrioid	12	10
Anaplastic	1	0
Adenocarcinoma	15	15
Other/unknown	18	23
Poorly differentiated disease, %	54	54

\*ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics.

### Treatment

Six cycles of chemotherapy were planned with intervals of 3 weeks between cycles and with the first cycle starting within 2 weeks of randomization. Docetaxel at 75 mg/m<sup>2</sup> was administered as a 1-hour intravenous infusion. Paclitaxel at 175 mg/m<sup>2</sup> was administered as a 3-hour intravenous infusion. In both arms, administration of the taxane was immediately followed by a 1-hour intravenous infusion of carboplatin to an AUC of 5, with the initial dose calculated according to the method described by Calvert (mg = [glomerular filtration rate + 25] × 5) (17), by use of <sup>51</sup>Cr-EDTA (edetic acid) to measure the glomerular filtration rate (18). This dose remained fixed for all cycles, unless toxicity necessitated a reduction.

All patients received oral dexamethasone at either 8 mg twice daily for 3 days, starting the day before docetaxel, or at 20 mg administered 12 and 6 hours before paclitaxel. One hour before paclitaxel administration, patients also intravenously received 10 mg of chlorpheniramine (or 50 mg of diphenhydramine) and 50 mg of ranitidine (or 300 mg of cimetidine). Antiemetics used were either 3 mg of granisetron or 8 mg of ondansetron.

Cycles were repeated in the absence of progressive disease or prohibitive toxicity. If maximal tumor cytoreduction had not been achieved during primary surgery, further surgery was permitted between cycles 3 and 4. Patients who underwent this interval cytoreductive surgery then continued chemotherapy postoperatively for three more cycles. After six cycles, patients with a partial or complete response but with elevated CA-125 levels could continue with single-agent carboplatin to an AUC of 7 for up to three additional cycles; continuing the taxane-platinum combination was prohibited. Patients completing first-line therapy ceased all cytotoxic treatments until progression.

### Dose and/or Schedule Modifications

We delayed treatment for up to 2 weeks if the neutrophil count was less than  $1.5 \times 10^9$  neutrophils per liter and the platelet count was less than  $100 \times 10^9$  platelets per liter on day 1 of each cycle. Prophylactic antibiotics in all subsequent cycles were recommended for complicated grade 4 neutropenia. The dose of docetaxel was reduced to 60 mg/m<sup>2</sup> or that of paclitaxel to 135 mg/m<sup>2</sup> for subsequent cycles in the event of prolonged or complicated grade 4 neutropenia. If this degree of hematologic toxicity reoccurred despite the dose reduction, we recommended granulocyte colony-stimulating factor at 300 mg/day for all subsequent cycles. We allowed the use of granulocyte colony-stimulating factor for persistent neutropenic fever. Carboplatin was reduced to an AUC of 4 for complicated grade 4 thrombocytopenia.

We also allowed treatment to be delayed for 2 weeks for mucositis of grade 3 or higher and skin toxicity of grade 2 or higher. In the event that liver function deteriorated or that neurotoxicity to grade 3 or higher occurred, we recommended that the taxane be discontinued. Patients could continue carboplatin alone if further chemotherapy was indicated.

For clinically significant hypersensitivity reactions to taxanes, the infusion was stopped, symptoms were treated, and patients were reinfused within 3 hours without further premedication if appropriate. Less severe reactions were managed by slowing down the infusion, observing the patient until recovery, and then reinfusing at the initial rate.

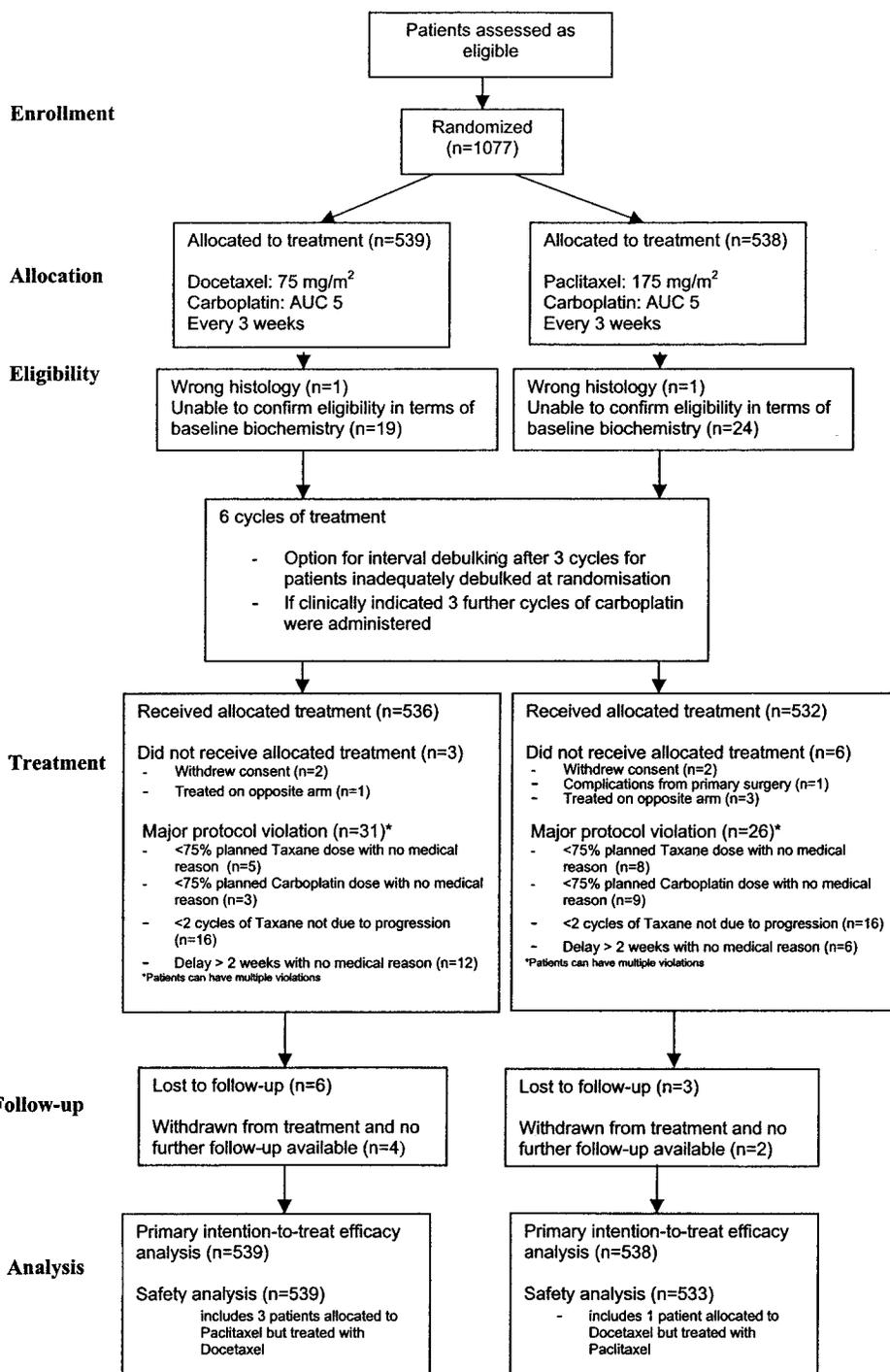


Fig. 1. Patients' progress through trial.

## Clinical Assessments

Before entry, patients underwent a physical examination, electrocardiogram, chest x-ray, abdominopelvic computed-tomography scan, full blood count, biochemical profile, CA-125 assay, and documentation of renal function via isotopic measurement, as previously described (18).

Patients had weekly full blood counts during chemotherapy, and the physical examination and assessments of ECOG performance status, biochemistry, and CA-125 level were repeated before each cycle. Response was assessed with a computed-tomography scan after cycles 3 and 6, and this procedure was also

recommended if CA-125 had increased or plateaued. The CA-125 response was classified according to the method of Rustin (19).

A complete response was defined as the complete disappearance of all measurable (in two dimensions) and evaluable disease, with no new lesions appearing, no disease-related symptoms, and no evidence of nonevaluable disease, including normalization of CA-125 level and other abnormal laboratory values. A partial response was defined as a 50% or greater decrease from baseline in the sum of products of perpendicular diameters of all bidimensionally measurable lesions, with no clinically significant increase in size of evaluable lesions and

with no new lesions. For a unidimensionally measurable tumor, a partial response was defined as a decrease of 50% or more in the sum of the largest diameters of all lesions. It was not necessary for all lesions to have regressed. Stable and/or no change was defined as a tumor that did not qualify for a complete response, a partial response, or progressive disease or had an unknown status. Progressive disease was defined as 1) a 25% or greater increase in the size of at least one bidimensionally or unidimensionally measurable lesion, 2) a clear worsening from previous assessment of any evaluable disease (note that worsening of existing nonevaluable disease did not constitute progression), 3) the reappearance of any lesion that had disappeared, with the exception of ascitic or pleural fluid that was drained and recurred within 3 months of drainage, or 4) the appearance of any new lesion and/or site.

Toxic effects were documented by use of the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Quality of life was prospectively evaluated before each cycle, at 6 months, and every 4 months for up to 2 years by use of the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 (version 3.0), and EORTC QLQ-OV28 (version 1) (20). In some centers, patients undertook a neurotoxicity assessment (21) that consisted of 12 questions and five neurologic tests (producing a neurotoxicity score [NScore]) at baseline, after cycles 3 and 6, at 6 months, and every 4 months for up to 2 years.

Follow-up for each patient occurred every 2 months, until the CA-125 level increased plus symptoms appeared or until radiologically defined disease progression. Physical examinations were given and CA-125 levels were determined every 2 months. Computed tomography scans were recommended in patients with no symptoms but increasing levels of markers. Follow-up intervals were extended after 2 years according to each center's local policy. Centers assessing NScore and quality-of-life data collected data until progression or up to a maximum of 2 years after treatment.

### Statistical Analysis

The primary study end point was progression-free survival. The study was designed with an 80% power to detect a difference of 25% in median progression-free survival (from 17 to 21.25 months) at the two-sided 5% level of statistical significance. This required 1050 patients with a minimum follow-up of 1 year.

Progression-free and overall survival were analyzed with the Cox model, incorporating study pretreatment factors used in randomization. Responses were compared by use of Fisher's exact test. The Mann-Whitney *U* test was used for safety analyses; for some toxic effects, the *U* test was supplemented by Fisher's exact test. All analyses for efficacy were performed on an intent-to-treat basis, and all patients were included for analysis wherever possible.

EORTC quality-of-life instrument measures were calculated (22) and grouped into the following four families of end points: global health status, functional scales, symptom scales, and neurotoxicity. The latter consisted of the NScore and the neurotoxicity scale from questionnaire QLQ-OV28. Analysis was further split into the following three time periods: acute effects (on treatment), persistent effects (change between 6 months and baseline), and long-term effects (change over follow-up period).

For each patient, the standardized area under the curve (36) compared with baseline was calculated; this end point was compared between the arms by use of the Wilcoxon two-sample test. Multiple testing within each family and/or time point combination was corrected for by the Hochberg (23) procedure. Multiple imputation (24) was applied to assess the robustness of the results to missing data. All statistical tests were two-sided.

## RESULTS

### Treatment Delivery

There were no statistically significant differences between arms for taxane and carboplatin dose intensity, cumulative dose, or the proportions of patients receiving carboplatin after completing the taxane-carboplatin combination. Eighty-two (15%) of the 539 patients receiving docetaxel-carboplatin and 114 (21%) of the 538 patients receiving paclitaxel-carboplatin withdrew from the protocol before completion, mostly because of toxicity. Neurotoxicity prompted the early withdrawal of 31 patients receiving paclitaxel-carboplatin but only of four patients receiving docetaxel-carboplatin. In the docetaxel-carboplatin arm, the most common reason for early withdrawal was hypersensitivity (12 patients). Sixty-eight (13%) of the 538 patients in the paclitaxel-carboplatin arm and 59 (11%) of the 539 patients in the docetaxel-carboplatin arm went on to receive an additional three cycles of carboplatin treatment (AUC of 7).

### Survival

At the time of analysis, 686 patients had progressed or died (343 on each study arm). The median was 23 months, and 98% of living patients had a minimum 1 year's follow-up. The median progression-free survival for the docetaxel-carboplatin arm was 15.0 months (95% confidence interval [CI] = 13.3 to 16.6) and for the paclitaxel-carboplatin arm was 14.8 months (95% CI = 13.5 to 16.1) (hazard ratio [HR] for docetaxel-paclitaxel = 0.97, 95% CI = 0.83 to 1.13; *P* = .707) (Fig. 2, A). The 2-year survival rates associated with docetaxel-carboplatin treatment and paclitaxel-carboplatin treatment were 64.2% (95% CI = 59.9% to 68.5%) and 68.9% (95% CI = 64.6% to 73.2%), respectively (HR for docetaxel-paclitaxel = 1.13, 95% CI = 0.92 to 1.39; *P* = .238) (Fig. 2, B).

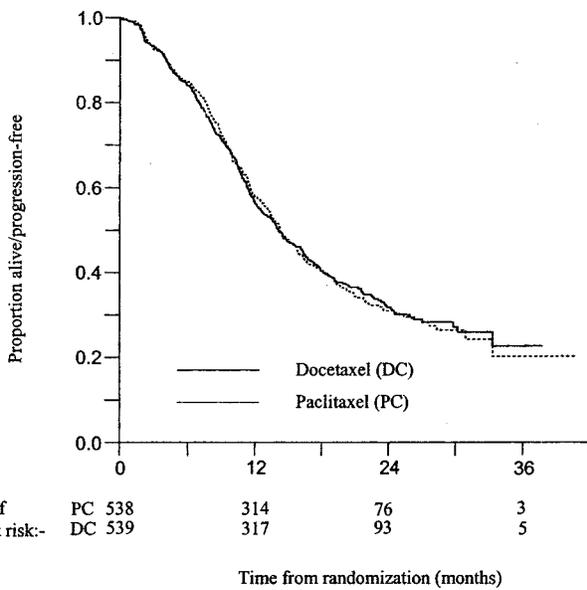
### Response

There was no statistically significant difference in clinical or CA-125 response rates, and 300 patients in the docetaxel-carboplatin arm and 296 patients in the paclitaxel-carboplatin arm were evaluable. Clinical response rates were 58.7% in the docetaxel-carboplatin arm and 59.5% in the paclitaxel-carboplatin arm (difference = -0.8%, 95% CI = -8.6 to 7.1; *P* = .868) (Table 2). The complete response rate was 28% in both arms. CA-125 responses could be evaluated in 68% of patients. Such responses occurred in 75.8% of the patients in the docetaxel-carboplatin arm and in 76.8% of the patients in the paclitaxel-carboplatin arm (difference = -1.0%, 95% CI = -7.2 to 5.1; *P* = .794).

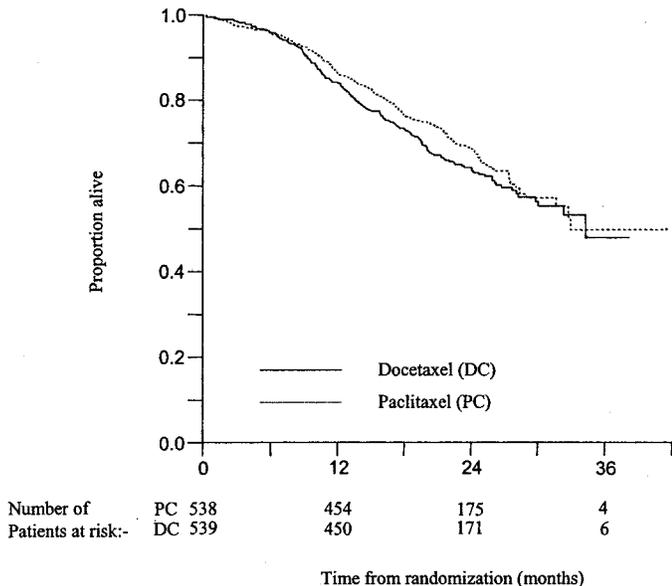
### Toxicity

Five patients (three in the paclitaxel-carboplatin arm and two in the docetaxel-carboplatin arm) did not start any treatment and

A



B



**Fig. 2.** Kaplan-Meier probability of progression-free survival (A) and overall survival (B). For paclitaxel-carboplatin (PC), the estimated percentage progression-free survival rates are at 1 year, 60% (95% confidence interval [CI] = 56% to 64%), at 2 years, 34% (95% CI = 29% to 38%), and at 3 years, 23% (95% CI = 14% to 32%). For docetaxel-carboplatin (DC), the estimated percentage of progression-free survival rates are at 1 year, 59% (95% CI = 55% to 63%), at 2 years, 35% (95% CI = 31% to 39%), and at 3 years, 26% (95% CI = 18% to 33%). For PC, the estimated percent survival rates are at 1 year, 86% (95% CI = 83% to 89%), 2 years, 69% (95% CI = 65% to 73%), and at 3 years, 50% (95% CI = 40% to 60%). For DC, the estimated percent survival rates are at 1 year, 84% (95% CI = 81% to 87%), at 2 years, 64% (95% CI = 60% to 68%), and at 3 years, 48% (95% CI = 36% to 60%).

were excluded from toxicity analyses. Three patients in the paclitaxel-carboplatin arm and one patient in the docetaxel-carboplatin arm were treated on the opposite arm and were analyzed for toxicity according to the treatment they actually received. The incidence of grade 3-4 neutropenia (94% versus 84%, difference = 11%, 95% CI = 7% to 14%;  $P < .001$ ) and of

**Table 2.** Best clinical and/or radiologic responses of patients in the Scottish Randomised Trial in Ovarian Cancer 1

	% of patients	
	Docetaxel-carboplatin arm (n = 300)	Paclitaxel-carboplatin arm (n = 296)
Objective response	59*	59*
Complete response	28	28
Partial response	30	31
No change	29	27
Progression	9	10
Missing data or unevaluable	4	4

\*Complete plus partial responses.

complicated neutropenia (grade 4 neutropenia for more than 7 days or with fever;  $P < .001$ ) was statistically significantly higher in the docetaxel-carboplatin arm than in the paclitaxel-carboplatin arm (Table 3). Two patients died as a result of toxicity in the docetaxel-carboplatin arm, whereas one died in the paclitaxel-carboplatin arm. Similar low rates of grade 3-4 nonhematologic toxicity (occurring in  $\geq 5\%$  of patients) were observed for both regimens (Table 4). Overall, we observed more gastrointestinal toxicities, peripheral edema, allergic reactions, and nail changes in the docetaxel-carboplatin arm and more arthralgia, myalgia, alopecia, and abdominal pain in the paclitaxel-carboplatin arm.

### Neurotoxicity

Treatment with docetaxel-carboplatin was associated with statistically significantly lower incidences of neurosensory (45% versus 78%;  $P < .001$ ) and neuromotor (9% versus 16%;  $P = .001$ ) toxicity than treatment with paclitaxel-carboplatin. Rates of grade 2-4 neurosensory toxicity were 11% in the docetaxel-carboplatin arm and 30% in the paclitaxel-carboplatin arm (difference = 19%, 95% CI = 15% to 24%;  $P < .001$ ). In addition, grade 2-4 neuromotor toxicity was statistically significantly ( $P < .001$ ) less frequent in the docetaxel-carboplatin arm (3%) than in the paclitaxel-carboplatin arm (7%; difference = 4%; 95% CI = 1% to 7%). These data are presented in Table 5.

### Quality of Life and NScore

Quality-of-life data were available for 974 patients and consisted of 6582 assessments; NScore data were available for 538 patients and consisted of 1854 assessments. (Only 64% of patients at the centers where this end point was analyzed completed the NScore assessment questionnaire because only a fixed number of NScore questionnaires was available at each site, and these questionnaires were not replaced when they ran out.) The completion rate was highest during therapy and lowest during follow-up, but the pattern of missing data over time did not differ markedly between treatment arms.

Global quality-of-life scores did not differ between treatment arms during either therapy or follow-up, with scores increasing from baseline in both arms. During therapy, there were no differences between treatment arms for virtually all the functional scores (performance, role, emotional, cognitive, and social functioning; body image; and attitude toward disease and treat-

**Table 3.** Hematologic toxicity and neutropenic complications of patients in the Scottish Randomised Trial in Ovarian Cancer 1

	% of patients		<i>P</i> *
	Docetaxel–carboplatin arm (n = 539)	Paclitaxel–carboplatin arm (n = 533)	
Grade 3–4 hematologic toxicity†			
Neutropenia	94	84	<.001
Thrombocytopenia	9	10	.595
Anemia	11	8	.112
Neutropenic complications			
Grade 4 neutropenia + fever	11	2	<.001
Grade 4 neutropenia >7 days	14	3	<.001

\*All statistical tests were two-sided. *P* values were from Fisher's exact test.

†No hematologic toxicity data were available for three patients (two in the paclitaxel–carboplatin arm and one in the docetaxel–carboplatin arm) who died after one cycle.

ment), apart from the body image quality-of-life variable, which deteriorated more in the paclitaxel–carboplatin arm than in the docetaxel–carboplatin arm (Table 6). Symptom scores showed that pain and gastrointestinal symptoms decreased more in the docetaxel–carboplatin arm and that hair loss, weakness, and aches and pains increased more in the paclitaxel–carboplatin arm. For neurotoxicity, the quality-of-life score deteriorated and the NScore increased more in the paclitaxel–carboplatin arm than in the docetaxel–carboplatin arm.

For persistent (baseline to 6 months) and long-term effects, the only measures associated with differences between treat-

ments were neuropathy and NScore. The increase in these measures associated with symptoms between 6 months and baseline was greater for the paclitaxel–carboplatin arm than for the docetaxel–carboplatin arm, and this difference persisted during follow-up. In all analyses, the patterns of missing data for quality of life and neurotoxicity were similar for both arms. Thus, the comparison between arms is unlikely to be biased, although, given the unblinded nature of the study, we cannot completely exclude this possibility. The imputation analysis, which yielded essentially the same results (Table 6), gives additional confidence in the robustness of the findings.

**Table 4.** Grade 3–4 nonhematologic toxicity occurring in at least 5% of patients on one treatment arm or where there was a statistically significant difference between arms (percentage of patients on each arm): the Scottish Randomised Trial in Ovarian Cancer 1\*

Toxicity	Arm†	NCI–CTC grade, No. of patients				<i>P</i>
		1	2	3	4	
Acute allergic reaction/hypersensitivity associated with taxane infusion	DC	8	8	3	0	<.001
	PC	4	3	1	1	
Diarrhea	DC	28	18	6	0	.001
	PC	24	12	3	0	
Nausea	DC	41	28	9	—	<.001
	PC	41	23	5	—	
Stomatitis	DC	28	19	2	0	<.001
	PC	21	11	0	0	
Taste disturbance	DC	18	13	—	—	<.001
	PC	12	9	—	—	
Vomiting	DC	14	15	7	1	.706
	PC	21	14	4	9	
Edema	DC	11	12	4	0	<.001
	PC	6	8	2	0	
Arthralgia	DC	13	6	1	0	<.001
	PC	16	14	2	0	
Myalgia	DC	12	7	1	0	<.001
	PC	17	13	3	0	
Alopecia	DC	18	75	—	—	<.001
	PC	7	89	—	—	
Nail changes	DC	11	5	—	—	<.001
	PC	1	0	—	—	
Abdominal pain or cramping	DC	14	12	4	1	.328
	PC	11	11	6	0	
Fatigue	DC	29	33	8	0	.105
	PC	27	30	8	0	
Constipation	DC	25	23	5	1	.065
	PC	26	27	5	0	
Sensory	DC	35	9	2	0	<.001
	PC	48	22	8	0	
Motor	DC	6	2	1	0	<.001
	PC	9	5	2	0	

\*DC = docetaxel–carboplatin treatment; PC = paclitaxel–carboplatin treatment; NCI–CTC = National Cancer Institute–Common Toxicity Criteria. — = none.

†There were 532 patients on PC and 537 patients on DC. No toxicity data were available for three patients (one in the docetaxel–carboplatin arm, who withdrew after one cycle, and two in the paclitaxel–carboplatin arm) who died after cycle 1.

**Table 5.** NCI-CTC neurotoxicity in the Scottish Randomised Trial in Ovarian Cancer 1\*

Grade	% of patients		P
	Docetaxel-carboplatin arm (n = 537)†	Paclitaxel-carboplatin arm (n = 532)‡	
<b>Sensory</b>			
1	35	48	<.001
2	9	22	
3	2	8	
4	0	0	
Total	45	78	<.001¶
<b>Motor</b> ¶¶			
1	6	9	.005
2	2	5	
3	1	2	
4	0	0	
Total	9	16	.001¶¶

\*NCI-CTC = National Cancer Institute-Common Toxicity Criteria.  
 †Not available for two patients who died after one cycle.  
 ‡Not available for one patient who died after one cycle.  
 §All statistical tests were two-sided. P value from Mann-Whitney U test.  
 ||Grades 1-4.  
 ¶¶Total.

## DISCUSSION

In this randomized controlled trial, we found that docetaxel-carboplatin treatment appeared to have efficacy similar to paclitaxel-carboplatin. Although exact equality can never be proven by clinical trials, the size of our study is large enough so that we can exclude the possibility that docetaxel treatment is associated with clinically significantly worse progression-free survival (maximum increase in the hazard rate with docetaxel is 13%, the upper bound of the 95% confidence interval) compared with

paclitaxel treatment. Both regimens produced similar response rates, and both were associated with acceptable toxicities. Docetaxel-carboplatin treatment was associated with statistically significantly more myelosuppression but statistically significantly less neurotoxicity than paclitaxel-carboplatin treatment during both therapy and follow-up.

Although preclinical studies indicated that docetaxel might be superior to paclitaxel, this study did not demonstrate a progression-free or overall survival advantage for docetaxel-carboplatin treatment over paclitaxel-carboplatin treatment, although the relatively short follow-up precludes a definitive statement on overall survival. These outcome data are consistent with those reported in other studies of treatment with paclitaxel-carboplatin in a heterogeneous mixture of chemotherapy-naive ovarian cancer patients (25,26). Longer survival times reported in other trials may reflect their inclusion of populations expected to do relatively well, e.g., patients with no residual disease after primary surgery (4). In addition, the broad definition of progressive disease in this trial is likely to produce shorter progression-free times than the definitions used in other studies.

Peripheral neurotoxicity [predominantly sensory but can progress to motor weakness (27)] is the principal nonhematologic toxicity of paclitaxel and may manifest early in the course of treatment (28). Reduced neurotoxicity without decreased antitumor efficacy has been shown when paclitaxel was combined with carboplatin rather than with cisplatin in major clinical trials in ovarian cancer (4,5); however, neurotoxicity is still experienced by many patients. Our data point to further improvement when paclitaxel is replaced by docetaxel. Neurotoxicity is infrequently reported during docetaxel therapy unless cumulative doses exceed 600 mg/m<sup>2</sup> (29). During this trial, neurotoxicity was more problematic than myelosuppression and was the leading reason for early withdrawal in the paclitaxel-carboplatin

**Table 6.** Quality-of-life and neurotoxicity scores: standardized area under the curve compared with baseline: Scottish Randomised Trial in Ovarian Cancer 1<sup>a</sup>

Time period/family	Parameter	Arm	No. of patients	Mean (95% CI)	Median (IQ range)	P <sup>b</sup>	
						Raw	Imputed
Acute/functional	Body image	PC	421	9.80 (7.47 to 12.13)	8.33 (0.00, 23.33)	.001	.001
		DC	424	5.14 (2.94 to 7.34)	3.33 (-5.63, 18.33)	***	***
Acute/symptom	Pain	PC	442	-5.89 (-7.95 to -3.83)	-3.75 (-16.67, 5.00)	<.001	<.001
		DC	454	-12.08 (-14.00 to -10.16)	-8.33 (-23.33, 0.00)	***	***
	Gastro-intestinal	PC	432	-6.64 (-8.25 to -5.03)	-4.44 (-15.56, 4.44)	<.001	.002
		DC	431	-10.36 (-11.97 to -8.75)	-7.22 (-20.00, 1.11)	**	**
	Hair loss	PC	419	57.63 (55.49 to 59.77)	58.33 (43.33, 76.67)	<.001	<.001
		DC	418	46.92 (44.51 to 49.33)	44.58 (27.78, 66.67)	****	****
	Weakness	PC	424	11.38 (9.17 to -13.59)	9.17 (0.00, 26.67)	<.001	<.001
		DC	424	4.82 (2.62 to 7.02)	3.33 (-1.67, 16.67)	****	***
	Aches and pains	PC	426	15.66 (13.45 to 17.87)	16.67 (0.00, 30.00)	<.001	<.001
		DC	420	5.52 (3.42 to 7.62)	3.33 (0.00, 18.33)	****	****
Acute/neurotoxicity	QoL	PC	427	22.45 (20.41 to 24.49)	16.67 (4.17, 36.67)	<.001	<.001
		DC	425	6.29 (4.94 to 7.64)	0.00 (0.00, 10.00)	****	****
	NScore	PC	181	2.46 (2.13 to 2.79)	2.27 (0.77, 4.00)	<.001	<.001
		DC	171	0.70 (0.48 to 0.92)	0.01 (0.00, 1.00)	****	****
Persistent/neurotoxicity	QoL	PC	251	32.93 (28.89 to 36.97)	33.33 (0.00, 66.67)	<.001	<.001
		DC	242	16.67 (13.10 to 20.24)	0.00 (0.00, 33.33)	****	****
	NScore	PC	119	3.83 (3.20 to 4.46)	4.00 (1.00, 6.38)	<.001	<.001
		DC	124	2.10 (1.47 to 2.73)	0.00 (0.00, 3.50)	****	****
Long-term/neurotoxicity	QoL	PC	242	23.27 (19.98 to 26.56)	16.67(0.00, 33.33)	<.001	.002
		DC	238	14.79 (11.69 to 17.89)	0.00(0.00, 29.05)	****	***
	NScore	PC	118	2.69 (2.14 to 3.24)	2.00 (0.34, 4.72)	.005	.018
		DC	111	1.69 (1.16 to 2.22)	1.00 (0.00, 3.00)	***	**

<sup>a</sup>DC = docetaxel-carboplatin; IQ = interquartile; NScore = neurotoxicity score; PC = paclitaxel-carboplatin; QoL = quality of life; acute = during treatment; persistent = at 6 months; long term = ≥8 months; CI = confidence interval. Positive differences in scores indicate a deterioration from baseline.

<sup>b</sup>Exact P values are given for initial tests. P values obtained from the Mann-Whitney U test. All statistical tests were two-sided. After the adjustment multiple testing within family of end points: \*\* = statistically significant at 5% level, \*\*\* = statistically significant at 1% level; \*\*\*\* = statistically significant at 0.1%.

arm. Our 30% rate of clinically significant neurotoxicity for the paclitaxel–carboplatin arm is higher than previously reported and may be attributable to our comprehensive approach to neurotoxicity monitoring.

There is a growing appreciation of the importance of quality-of-life measures in cancer patients because the goals of therapy are to improve the quality as well as the duration of life. Generic quality-of-life measures do not adequately address disease- and treatment-related issues in ovarian cancer, and the OV28 instrument has been developed specifically for this unmet need (20). The improvements in quality-of-life parameters in the docetaxel–carboplatin arm, compared with the paclitaxel–carboplatin arm, as shown by validated instruments specific to ovarian cancer patients, are therefore of considerable interest. During therapy, pain and gastrointestinal quality-of-life scores decreased more in the docetaxel–carboplatin arm, whereas hair loss, weakness, and aches and pains increased more in the paclitaxel–carboplatin arm. Body image also deteriorated more in the paclitaxel–carboplatin arm at 6 months and on long-term follow-up than in the docetaxel–carboplatin arm; the two groups also differed with respect to neurotoxicity and NScore. It should be noted that the gastrointestinal quality of life score relates more to symptoms of disease (bloating, abdominal pain, feeling full) than the side effects of treatment, which is why it tends to improve during treatment.

The results of Osabe et al. (35) provide a basis for interpreting the differences between the two patient groups; broadly, that report suggested that patients regard differences of between 5 and 10 in EORTC quality-of-life scales as small, 10–20 as moderate, and greater than 20 as large. By these criteria, the differences between the arms with regard to hair loss and aches and pains and quality of life neurotoxicity (acute/persistent) are moderate; the remaining differences are all small.

The difference in mean NScore between successive grades of the NCIC–CTC toxicity scale is approximately 3.0 (data on file, Cancer Research U.K. Trials Unit, Glasgow, U.K.); this difference can be used to interpret the clinical significance of the mean difference between the arms in the acute (mean difference = 1.76), persistent (mean difference = 1.73) and long-term (mean difference = 1.00) time periods. These results clarify the effect of neurotoxicity on quality of life, which has been poorly elucidated to date through the use of validated and reliable instruments (27); support earlier results that showed a low incidence of neuropathy in ovarian cancer patients who received docetaxel (16,17); and concur with the observation that neurotoxicity is less severe with docetaxel than with paclitaxel and is not dose-limiting (30).

Neurotoxicity data from SCOTROC 1 have been independently incorporated into a retrospective study evaluating quality-of-life effects of chemotherapy-induced neuropathy compared with other symptoms of ovarian cancer and its treatment (31). Key findings of this study were that clinically significant neuropathy was experienced by 57% of cisplatin-treated patients and 62% of paclitaxel-treated patients, reducing quality of life by 17% to 24%. By analyzing preliminary SCOTROC data, it was estimated (31) that severe chemotherapy-induced neuropathy reduced quality of life by 10% to 20%.

Statistically significantly more grade 3–4 neutropenia but no increased mortality was associated with docetaxel–carboplatin treatment compared with paclitaxel–carboplatin. Although there were higher incidences of complicated myelotoxicity with do-

cetaxel–carboplatin, overall rates were low (approximately 10%) and did not compromise dose delivery or safety. In addition, the widespread use of prophylactic antibiotics and the availability of colony-stimulating factors allowed for the safe administration of myelosuppressive chemotherapy; furthermore, another study (17) suggested that the reduction of docetaxel to 60 mg/m<sup>2</sup> was unlikely to affect survival.

The research efforts of the Scottish Gynaecological Cancer Trials Group have shifted toward the evaluation of sequential chemotherapy regimens consisting of four cycles of single-agent carboplatin at a higher AUC of 7 followed by four cycles of docetaxel-based therapy. The results of ongoing feasibility trials of this approach [SCOTROC 2 program (32,33)] will be analyzed together to form the basis of a future phase III trial that will explore the merits of this type of sequential treatment relative to conventionally delivered concurrent chemotherapy.

In conclusion, treatment with docetaxel–carboplatin should be viewed as an alternative to treatment with paclitaxel–carboplatin for newly diagnosed stage Ic–IV ovarian cancer. Treatment with docetaxel–carboplatin provides a similar level of progression-free survival to treatment with paclitaxel–carboplatin while reducing the level of neurotoxicity and improving the level of treatment-related quality of life.

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## NOTES

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