A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer

Andreas du Bois, Hans-Joachim Lück, Werner Meier, Hans-Peter Adams, Volker Möbus, Serban Costa, Thomas Bauknecht, Barbara Richter, Matthias Warm, Willibald Schröder, Sigrid Olbricht, Ulrike Nitz, Christian Jackisch, Günther Emons, Uwe Wagner, Walther Kuhn, Jacobus Pfisterer

For the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group

Background: **Despite considerable improvement in the treatment of advanced ovarian cancer, the optimization of efficacy and tolerability remains an important issue. Therefore, we performed a randomized, phase III non-inferiority trial comparing paclitaxel plus cisplatin (PT) with paclitaxel plus carboplatin (TC) in patients with advanced ovarian cancer.** ***Methods:*** **A total of 798 patients with International Federation of Gynecology and Obstetrics stage IIB–IV were randomly assigned to receive six courses of either PT or TC at 3-week intervals. The primary endpoint was the proportion of patients without progression at 2 years. Secondary endpoints included toxicity, response to treatment, quality of life, and overall and progression-free survival time. Quality of life was evaluated using the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ)-C30, version 2.0. Survival curves were calculated using the Kaplan–Meier method, and hazard ratios were estimated using the Cox proportional hazards model.** ***Results:*** **The proportion of patients without progression at 2 years was not statistically significantly different between the two treatment arms (40.0% for PT versus 37.5% for TC, difference = 2.5%, one-sided 95% confidence interval [CI] = −∞ to 8.2%). Median progression-free survival time in the TC arm (17.2 months, 95% CI = 15.2 to 19.3 months) and the PT arm (19.1 months, 95% CI = 16.7 to 21.5 months) were also not statistically significantly different; the same was true of median overall survival time (43.3 months, 95% CI = 37.2 to 47.8 months versus 44.1 months, 95% CI = 40.2 to 49.4 months, for the TC and PT arms, respectively). The TC regimen was associated with a higher frequency of hematologic toxicity, but a lower frequency of gastrointestinal and neurologic toxicity, than the PT regimen. Mean global quality-of-life scores at the end of treatment were statistically significantly better in the TC arm than in the PT arm (65.25 versus 51.97, respectively; difference = –13.28, 95% CI = –18.88 to –7.68).** ***Conclusion:*** **The TC regimen achieved comparable efficacy to the PT regimen but was associated with better tolerability and quality of life, and should, therefore, be considered as an important alternative for standard first-line chemotherapy in patients with advanced ovarian cancer. [J Natl Cancer Inst 2003;95:1320–30]**

During the past two decades, the chemotherapy regimens used to treat advanced ovarian cancer have undergone two major advances in efficacy, the first being the introduction of platinum-based agents and the second the introduction of taxanes. In the mid-1980s, two studies *(1,2)* demonstrated that the addition of cisplatin to the combination of doxorubicin and cyclophosphamide (CAP) statistically significantly increased response rates and progression-free and overall survival times. Subsequent studies *(3,4)* have not shown any clinically relevant differences in efficacy between two-drug combinations (predominantly cisplatin and cyclophosphamide) and multidrug combinations, which for the most part included anthracyclines. As a result, the combination of cisplatin and cyclophosphamide was considered standard therapy for the first-line treatment of patients with advanced ovarian cancer for approximately the next 10 years.

The replacement of cyclophosphamide with paclitaxel in first-line therapy marked the next major advance in treatment efficacy for advanced ovarian cancer, as first reported in a study by the Gynecologic Oncology Group (GOG) *(5)* and confirmed by a European–Canadian intergroup study *(6).* The paclitaxel-

Affiliations of authors: A. du Bois, Department of Gynecology and Gynecologic Oncology, Dr.-Horst-Schmidt-Kliniken, Wiesbaden, Germany, and Department of Gynecology and Obstetrics, St.-Vincentius-Hospital, Karlsruhe, Germany; H.-J. Lück, Department of Gynecologic Oncology, Medizinische Hochschule, Hannover, Germany; W. Meier, Department of Gynecology and Obstetrics, University München-Groβhadern, Germany; H.-P. Adams, Methodisches Zentrum–GynDat, Dr.-Horst-Schmidt-Kliniken, Wiesbaden; V. Möbus, Department of Gynecology and Obstetrics, University of Ulm, Germany; S. Costa, Department of Gynecology and Obstetrics, University of Frankfurt, Germany; T. Bauknecht, Department of Gynecology and Obstetrics, University of Freiburg, Germany; B. Richter, Department of Gynecology and Obstetrics, University of Dresden, Germany; M. Warm, Department of Gynecology and Obstetrics Klinikum, Stralsund, Germany; W. Schröder, Department of Gynecology and Obstetrics, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany; S. Olbricht, Department of Gynecology and Obstetrics, Medizinische Akademie, Magdeburg, Germany; U. Nitz, Department of Gynecology and Obstetrics, University of Düsseldorf, Germany; C. Jackisch, Department of Gynecology and Obstetrics, University of Münster, Germany; G. Emons, U. Wagner, Department of Gynecology, University of Marburg, Germany; W. Kuhn, Department of Gynecology and Obstetrics, University München rechts der Isar, Germany; J. Pfisterer, Department of Gynecology and Obstetrics, University Kiel, Germany.

Correspondence to: Andreas du Bois, MD, PhD, Dr.-Horst-Schmidt-Kliniken, Dept. of Gynecology and Gynecologic Oncology, Ludwig-Erhard-Str. 100, D-65199 Wiesbaden, Germany (e-mail: dubois.hsk-wiesbaden@uumail.de).

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plus-cisplatin combination regimen was superior to the cyclophosphamide-plus-cisplatin regimen in terms of response rate and progression-free and overall survival times. In the intergroup study *(6),* the administration of paclitaxel as a 3-hour infusion was based on the results of an international randomized trial *(7)* that observed comparable efficacy for 3-hour and 24-hour infusion of paclitaxel for recurrent ovarian cancer. As a result of the GOG *(5)* and the intergroup *(6)* confirmation trials, the combination of paclitaxel plus cisplatin became the standard therapy for first-line treatment of patients with ovarian cancer. However, this standard has been challenged recently by the International Collaborative Ovarian Neoplasm (ICON) 3 trial *(8),* in which paclitaxel plus carboplatin (TC) was compared with either single-agent carboplatin or CAP. The non-superiority of CAP or TC with single-agent carboplatin in terms of progression-free and overall survival is a matter of debate, and a confirmatory trial is eagerly awaited.

Despite increasing survival rates, advanced ovarian cancer is rarely cured and more than 50% of patients die within 5 years of their initial diagnosis *(1,5).* Therefore, tolerability of treatment and quality of life remain important issues in future research. Studies *(9,10)* have shown that, when carboplatin is combined with cyclophosphamide, it is better tolerated than cisplatin combined with cyclophosphamide, with no loss of efficacy. Because it was assumed that carboplatin plus paclitaxel might also be better tolerated than cisplatin plus paclitaxel, six phase I/II studies *(11–16)* were initiated to test the feasibility of the paclitaxel-plus-carboplatin combination as first-line therapy for patients with advanced ovarian cancer. The maximum tolerated dose of paclitaxel in each of these studies ranged from 175 to 275 mg/m^2, whereas the maximum tolerated dose of carboplatin ranged from 300 to 550 mg/m^2 or, when using the area under the curve (AUC) method, AUC 5 to AUC 7.5.

Because of the feasibility, promising efficacy, and acceptable toxicity of the TC regimen in these phase I/II studies, two large randomized phase III clinical trials were initiated: GOG protocol 158 *(17)* and the present study, protocol OVAR-3 of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group. Both trials were designed as non-inferiority trials to test the hypothesis that the tolerability advantage that carboplatin has over cisplatin is maintained in combination with paclitaxel, without affecting efficacy. We report the results of the AGO protocol OVAR-3 trial—the first, to our knowledge, large randomized clinical trial comparing the combination of cisplatin plus paclitaxel with the combination of paclitaxel plus carboplatin in patients with advanced ovarian cancer.

Patients and Methods

Patients and Study Design

Patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) *(12)* stages IIB–IV ovarian cancer were eligible for inclusion in this study. Patients had to have undergone radical debulking surgery within 6 weeks of random assignment. At study entry, all patients had to be at least 18 years of age and were required to have adequate hematologic, renal, and hepatic function, defined as follows: absolute neutrophil count (ANC) of at least 1.5×10^9 cells/L, platelet count of at least 100×10^9 cells/L, serum creatinine and bilirubin of no more than 1.25 × upper normal limit. Patients were excluded from the study if they had ovarian tumors with low malignant potential; an Eastern Cooperative Oncology Group performance status of more than 2 or a Karnofsky index of less than 60%; an estimated glomerular filtration rate (GFR) of less than 60 mL/minute; other malignancies; previous chemo-, immuno-, or radiotherapy for ovarian cancer; severe neuropathy; cardiac arrhythmias; or congestive heart failure.

After patients were randomly assigned to one of the treatment arms, there was no blinding of treatment allocation to investigators or patients. Patients were stratified into one of two *a priori* strata according to residual tumor size and FIGO stage *(12).* Stratum 1 contained patients with a residual tumor size of less than or equal to 1 cm and who were FIGO stage IIB, IIC, or III. Stratum 2 contained patients with a residual tumor size of more than 1 cm or who were FIGO stage IV. Within each stratum, randomization lists for each study center were prepared before the start of the trial using permuted blocks of randomly varying size. Patients were randomly assigned and stratified by the AGO-OVAR study office (Karlsruhe, Germany) based on patient data that the participating study centers provided. All participating centers were regularly monitored by trained field monitors who checked all of the data collected on case review forms against the medical records for each patient (i.e., 100% monitoring); these checks included review of the surgeon's and pathologist's reports. Quality-assurance measures consisted of double data entry and extensive programmed plausibility checks.

The study was designed and carried out in accordance with good clinical practice guidelines, German drug laws, relevant laws regarding how to conduct clinical studies, and the Declaration of Helsinki. German and Austrian centers (*see* "Appendix") of the AGO-OVAR participated in this study, and the local ethics committee of each participating center approved the study. This study was also certified by the German Cancer Society. All patients provided written informed consent before entry into the study.

Treatment Regimens

Patients were randomly assigned to receive paclitaxel plus carboplatin (TC arm) or paclitaxel plus cisplatin (PT arm). Patients in the TC arm received paclitaxel (185 mg/m^2) administered intravenously over 3 hours, followed by carboplatin (AUC 6) administered intravenously over 30–60 minutes. The carboplatin dose was calculated using the method of Calvert et al. *(13),* in which the required dose is obtained by the formula: carboplatin dose (in milligrams) = AUC × (GFR + 25). The GFR was estimated using the Jelliffe formula *(14).* We used this treatment schedule because it has been found to be the maximal tolerated dose in a preceding phase I/II trial *(11).* Patients in the PT arm received paclitaxel at the same dose and schedule as patients in the TC arm, followed by cisplatin (75 mg/m^2) administered intravenously over 30 minutes *(5,6).* Regardless of calculated doses, the maximal absolute dose that was given to each patient was limited to 400 mg for paclitaxel, 880 mg for carboplatin, and 165 mg for cisplatin.

Dose reductions were allowed depending on predefined levels of hematologic or non-hematologic toxicity, with dose reduction levels as follows: carboplatin AUC 5 (level 1) or AUC 4 (level 2), cisplatin at 60 mg/m^2 (level 1) or 50 mg/m^2 (level 2), and paclitaxel at 160 mg/m^2 (level 1) or 135 mg/m^2 (level 2). Any subsequent treatment cycle was delayed when the patient's

ANC was less than 1.5×10^9 cells/L or her platelet count was less than 100×10^9 cells/L. Primary prophylaxis using granulocyte colony-stimulating factor (G-CSF) was not allowed; however, supportive G-CSF treatment could be initiated at the discretion of the investigator if the patient's ANC recovery took more than 36 days.

All patients received premedication consisting of a single dose of dexamethasone (20 mg), clemastine (2 mg), and cimetidine (300 mg) administered 30 minutes before the start of the paclitaxel infusion. Anti-emetic prophylaxis consisted of serotonin type 3 receptor antagonists and corticoids. In addition, patients in the PT arm received pre- and post-chemotherapy hydration to avoid cisplatin-induced nephrotoxicity. Chemotherapy cycles were repeated every 3 weeks. Patients with disease progression during therapy went off protocol treatment. Patients who achieved partial remission and who exhibited residual tumor after six treatment cycles could receive additional treatment cycles if recommended by their physician. The same treatment rules applied to all cycles.

Toxicity and Quality-of-Life Measures

Adverse events and toxicities were graded by study investigators according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) *(15,16).* All observed toxicities were recorded continuously; blood-chemistry parameters were measured before each treatment cycle, and hematologic parameters were measured weekly. Quality of life was evaluated using global health status/quality-of-life score from the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-C30, version 2.0 *(18).* No specific QLQ module for ovarian cancer was used in this trial because one was not available at the time of the trial. Patients assessed their own health-related quality of life after every other treatment cycle, after the last treatment cycle, and 3 and 6 months after cessation of treatment. Quality-of-life responses were evaluated according to EORTC guidelines *(19).* Tumor measurements were taken before each treatment cycle by physical examination, before every third treatment cycle by imaging methods in patients with measurable or evaluable disease, and after the last treatment cycle. The same tumor assessment methods (i.e., ultrasound, x-ray, computed tomography, or magnetic resonance imaging) that were used for baseline measurement were also used for each repeat evaluation. Tumor response was graded according to the definitions of the World Health Organization *(20).* Second-look surgery was not recommended. Follow-up visits were scheduled every 3 months in the first 2 years after cessation of treatment and every 6 months thereafter, for a total follow-up time of 5 years.

Outcome Measures

The primary endpoint of this trial was the proportion of patients without disease progression at 2 years. Secondary endpoints included toxicity, quality of life, overall survival time, progression-free survival time, and response to treatment. Toxicity was measured by examining the frequency of grade 3/4 toxicities resulting from determination of maximum grade toxicities over all courses within patients (set P). In addition, grades of hematologic toxicities over all courses (set C) were analyzed. Intra-individual differences in quality-of-life scores at various time points (minus baseline values so that each patient serves as her own control) were calculated to ascertain whether changes in quality-of-life scores in the overall patient population were similar to changes within each patient. Overall survival time was calculated from the time of random assignment until death from any cause or to the date of last follow-up. Progression-free survival time was calculated from the time of random assignment until the date of documented disease progression. The occurrence of a secondary malignancy or death from any cause was also considered as disease progression.

Statistical Analysis

The sample size estimated for this non-inferiority trial, 692 patients, was calculated to exclude a difference between the proportions of patients without progression of disease at 2 years in the TC and PT arms of more than 8% (one-sided 95% confidence intervals [CIs] = ∞ to 8%), with $\alpha = .05$ and $\beta = .80$. This calculation was based on the assumption of an equal number of patients in stratum 1 and stratum 2 and a dropout rate of 10% during the first 2 years of the study. However, the sample size was increased to 798 during the trial to account for the higher proportion of patients in stratum 1. This amendment of the sample size was made without interim analysis.

Corresponding to the non-inferiority design, results are presented as differences in proportions or means with their 95% confidence intervals *(21,22).* The underlying hypothesis of a non-inferiority or equivalence trial is that there are two different patient populations. It is the goal of the trial to show whether these two patient populations differ in terms of outcome measures by more than some chosen difference in these outcome measures. The differences in proportions and means were always calculated by subtracting the result for the TC arm from the result for the PT arm. The 95% confidence intervals are always two-sided, except for the difference in the proportions of patients without progression of disease at 2 years, because the hypothesis of the trial was explicitly stated as one-sided. Proportions or means were considered to be statistically significantly different if the 95% confidence interval on the difference did not include zero, an estimate that is mathematically equivalent to a two-sided P value of less than .05. Overall and progression-free survival times were calculated using the Kaplan–Meier method *(23),* and hazard ratios (HRs) were estimated using the Cox proportional hazards model *(24).* Hazard ratios were considered to be statistically significantly different if the 95% confidence interval on the ratio did not include 1; again, an estimate that is considered to be mathematically equivalent to a two-sided P value of less than .05. All calculations were performed using SAS software (version 8.3; SAS Institute, Cary, NC). All analyses were performed on an intention-to-treat basis.

Results

Characteristics of Patients

Between November 1995 and November 1997, 883 patients were screened by the AGO-OVAR study office (Fig. 1). Of these, 9.6% (85/883) were not enrolled because of low GFR (n = 42), histology of non-epithelial ovarian cancer (n = 14), second malignancies (n = 8), concomitant diseases not allowing study participation (n = 8), planned interval surgery (n = 6), surgery more than 6 weeks before study entry (n = 3), or other reasons (n = 4). A total of 798 patients remained, of whom 350 fulfilled the criteria of stratum 2 and 448 fulfilled the criteria for stratum 1. Fifteen of the 798 (1.9%) randomly assigned patients

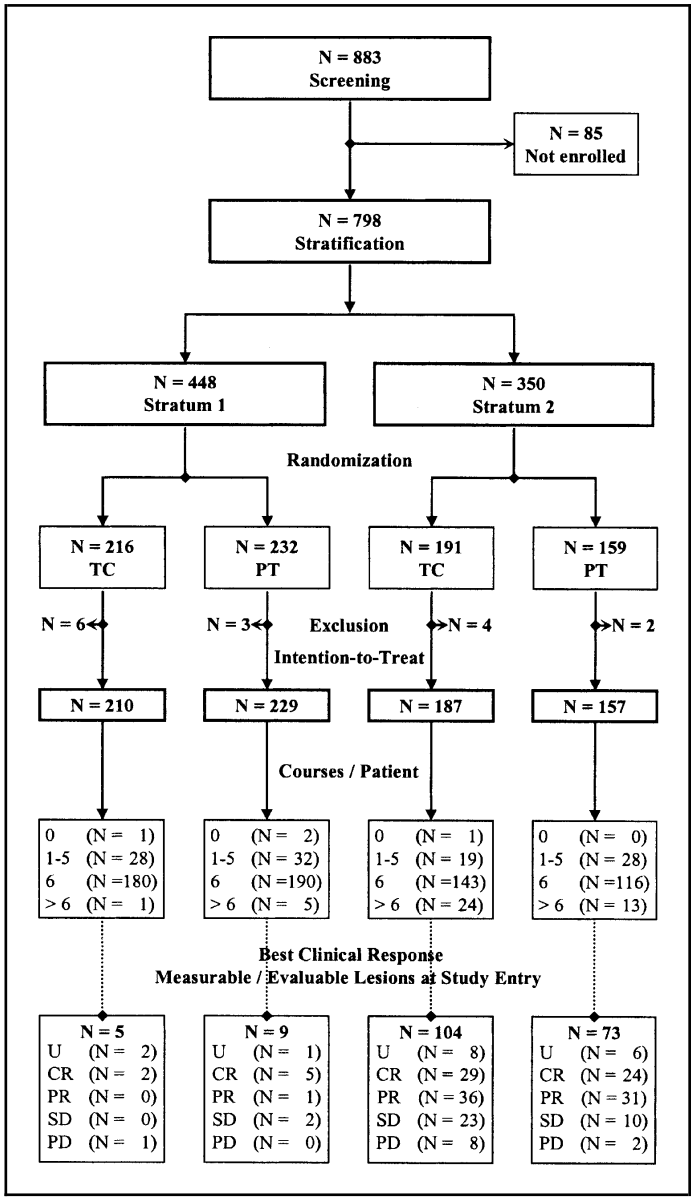

Fig. 1. CONSORT trial flow diagram for patients with advanced ovarian cancer. Patients were initially stratified into one of two *a priori* strata according to residual tumor size and stage (stratum 1: residual tumor size of ⩽1 cm and International Federation of Gynecology and Obstetrics [FIGO] stages IIB–III; stratum 2: residual tumor size of >1 cm or FIGO stage IV). Patients were then randomly assigned to receive either paclitaxel-plus-carboplatin combination treatment (TC) or cisplatin-plus-paclitaxel combination treatment (PT). The number of patients (N) with measurable/evaluable lesions at study entry is shown at the **top of the lower panels** for each treatment arm. The number of patients and their best clinical response is shown at the **bottom of the lower panels.** Best clinical response is defined as follows: U = unknown, CR = complete response, PR = partial response, SD = stable disease, PD = disease progression.

were excluded from the analysis because of violations of inclusion criteria (first detected at in-house monitoring sessions), including wrong FIGO stage (n = 2), non-epithelial ovarian or non-ovarian primary cancer (n = 2), second malignancies (n = 4), a GFR of less than 60 mL/minute (n = 2), pre-existing grade 2 neuropathy (n = 1), pre-existing LOWN *(25)* grade III arrhythmia (n = 1), withdrawal of consent (n = 2), and disease progression before start of treatment (n = 1). A total of 386 patients were enrolled in the PT arm, and 397 patients were enrolled in the TC arm. Eight of the 386 (2.1%) patients originally allocated to the PT arm crossed over to the TC arm for toxicity reasons. No patient in the TC arm crossed over to the PT arm.

Treatment arms were well balanced in terms of baseline characteristics (Table 1). The mean age of patients was 56.7 years (standard deviation [SD] = 10.93 years; range = 20.8–77.4 years) and 57.7 years (SD = 10.11 years; range = 25.4–83.6 years) in the TC and PT arms, respectively. Only 191 patients (23.9%) had measurable disease on study, which qualified them for evaluation of response to treatment. Of those 191 patients, response to treatment (according to protocol) was determined in 174 (91.1%). Response to treatment status was classified as unknown in 10 (5.2%) and 7 (3.7%) patients in the TC and PT arms, respectively, because the diagnostic tools used in the baseline and response assessments of these patients differed.

Treatment Compliance

Overall, 4438 treatment cycles were administered, 2274 in the TC arm and 2164 cycles in the PT arm, and most patients (87.7% in the TC arm and 84.0% in the PT arm; 85.8% overall) received at least six treatment cycles. Only 25 patients in the TC arm and 18 patients in the PT arm received more than six treatment cycles, and these patients were predominantly FIGO stage IV or had a residual tumor of more than 1 cm (Fig. 1 and Table

Table 1. Baseline patient characteristics*

	TC arm		PT arm		Total	
Characteristic	N	%	N	%	N	%
No. of patients	397	50.7	386	49.3	783	100.0
FIGO stage†						
IIB	13	3.3	12	3.1	25	3.2
IIC	24	6.0	17	4.4	41	5.2
IIIA	24	6.0	34	8.8	58	7.4
IIIB	53	13.4	42	10.9	95	12.1
IIIC	211	53.1	219	56.7	430	54.9
IV	72	18.1	62	16.1	134	17.1
Post-operative residual tumor						
Unknown	2		2		4	
⩽1 cm	235	59.5	253	65.9	488	62.6
>1 cm	160	40.5	131	34.1	291	37.4
Stratification‡						
Stratum 1	210	52.9	229	59.3	439	56.1
Stratum 2	187	47.1	157	40.7	344	43.9
Histology						
Serous/papillary	281	70.8	270	69.9	551	70.4
Other	116	29.2	116	30.1	232	29.6
Histologic grading§						
Unknown	20		13		33	
G1	36	9.5	25	6.7	61	8.1
G2	145	38.5	139	37.3	284	37.9
G3	196	52.0	209	56.0	405	54.0
Performance status at study entry‖						
ECOG 0	198	49.9	191	49.5	389	49.7
ECOG 1	166	41.8	159	41.2	325	41.5
ECOG 2	33	8.3	36	9.3	69	8.8

*TC = paclitaxel/carboplatin combination treatment; PT = cisplatin/paclitaxel combination treatment. Unknown values are excluded from sums and percentages.

†FIGO stage = International Federation of Gynecology and Obstetrics *(12)*.

‡Stratification consisted of two strata: Stratum 1 = residual tumor size less than or equal to 1 cm and FIGO stages IIB–III. Stratum 2 = residual tumor size of more than 1 cm or FIGO stage IV.

§Histologic grading was determined by each center's pathologist. The protocol did not require adherence to a specific grading system.

‖ECOG = Eastern Cooperative Oncology Group performance status.

2). The mean treatment interval was 22.8 days in the TC arm and 22.2 days in the PT arm. Overall, there were 3612 (cycles 1–6) treatment intervals, 1851 in the TC arm and 1761 in the PT arm. Treatment delays of at least 7 days occurred in 12.2% of all treatment intervals, and occurred statistically significantly more frequently in the TC arm than in the PT arm (14% versus 10.3%, respectively; difference in proportions = 3.7%, 95% CI = 1.6% to 5.8%).

Dose reductions were performed infrequently. Overall, only 82 patients (10.9%) received at least one dose reduction (Table 2). There was no statistically significant difference between the treatment arms in the percentage of patients with dose reductions (10.5% in the PT arm versus 11.2% in the TC arm; difference in proportions = –0.7%, 95% CI = –5.2% to 3.7%). The mean paclitaxel doses for all cycles in the TC and PT arms were 182.2 mg/m^2 and 182.8 mg/m^2, respectively. Corresponding mean platinum doses were 73.6 mg/m^2 for cisplatin and AUC 5.7 for carboplatin, respectively. A dose intensity higher than 90% was reached in both the TC and PT arms.

Treatment Toxicity

To determine hematologic (Table 3) and non-hematologic (Table 4) toxicities, patients were evaluated for adverse events and toxicity using the NCI CTC *(15,16)*. Grade 3/4 hematologic toxicities were statistically significantly more frequent in the TC arm than they were in the PT arm, including platelets, transfusion packed red blood cells, leukocytes, neutrophils, and febrile neutropenia (Table 3). Despite the higher frequency of thrombocytopenia (i.e., platelet count) in the TC arm than in the PT arm (3% versus 0.2%, respectively; difference in proportions = –2.8%, 95% CI = –3.6% to –2.1%), no severe hemorrhage was observed. The most frequent grade 3/4 hematologic side effect of treatment was neutropenia, whereas the least frequent was febrile neutropenia.

Grade 3/4 non-neutropenic infections, mostly urinary tract or minor postoperative wound infections, occurred more frequently in the TC arm than in the PT arm (35.6% versus 22.6%, respectively; difference in proportions = –12.9%, 95% CI = –19.3% to –6.6%; Table 4). Consequently, G-CSF was given statistically significantly more often to patients in the TC arm than to patients in the PT arm (6.0% versus 1.8%, respectively; difference in proportions = –4.2%, 95% CI = –5.5% to –3.0%; Table 3). However, myelosuppression was manageable in the majority of patients and did not result in a higher incidence of premature discontinuance of treatment, treatment delay, or dose reduction in patients in the TC arm. Furthermore, the need for antibiotic

Table 2. Therapy and efficacy parameters in patients with advanced ovarian cancer by treatment arm*

	TC arm		PT arm		Total		Difference† in the proportions of patients, %	
Parameters	N	%	N	%	N	%	E	95% CI
No. of treatment cycles received								
0	2	0.5	2	0.5	4	0.5	0.0	–1.3 to 1.3
1–5	47	11.8	60	15.5	107	13.7	3.7	–2.4 to 9.8
6	323	81.4	306	79.3	629	80.3	–2.1	–9.2 to 5.0
>6	25	6.3	18	4.7	43	5.5	–1.6	–5.7 to 2.4
Dose reduction for any reason								
Unknown	14		15		29			
No	340	88.8	332	89.5	672	89.1	0.7	–3.7 to 5.2
Yes	43	11.2	39	10.5	82	10.9	–0.7	–5.2 to 3.7
Treatment delay, days								
Unknown	2		2		4			
0	1586	69.7	1625	75.1	3211	72.4	5.3	2.0 to 8.7
1–6	422	18.6	355	16.4	777	17.5	–2.2	–5.0 to 0.7
⩾7	266	11.7	184	8.5	450	10.1	**–3.2**	**–5.4 to –1.0**
Subtotal	2274	51.2	2164	48.8	4438	100.0		
Clinical response‡								
Not evaluable	10		7		17			
Complete	31	31.3	29	38.7	60	34.5	7.4	–10.9 to 25.6
Partial	36	36.4	32	42.7	68	39.1	6.3	–12.4 to 25.0
Stable disease	23	23.2	12	16.0	35	20.1	–7.2	–22.2 to 7.7
Progressive disease	9	9.1	2	2.7	11	6.3	–6.4	–15.0 to 2.2
Subtotal	99	56.9	75	43.1	174	100.0		
Pathologic response at second-look operation								
Complete	27	36.5	26	43.3	53	39.6	6.8	–14.4 to 28.1
Partial	31	41.9	20	33.3	51	38.1	–8.6	–29.4 to 12.3
Stable disease	8	10.8	6	10.0	14	10.4	–0.8	–14.0 to 12.4
Progressive disease	8	10.8	8	13.3	16	11.9	2.5	–11.7 to 16.7
Subtotal	74	55.2	60	44.8	134	100.0		
Progression of disease at 2 y								
Unknown	8		6		14			
No	146	37.5	152	40.0	298	38.8	2.5	–4.4 to 9.4
Yes	243	62.5	228	60.0	471	61.2	–2.5	–9.4 to 4.4
Subtotal	389	50.6	380	49.4	769	100.0		

*TC = paclitaxel/carboplatin combination treatment; PT = cisplatin/paclitaxel combination treatment; E = estimate; CI = confidence interval. Unknown values are excluded from sums and percentages. N = number of patients, except for the treatment delay parameter, where N = the number of cycles.

†Differences are calculated by subtracting the TC arm proportion from the PT arm proportion; statistically significant differences are bold. All percentages are rounded; therefore, the estimates may differ by ±.1 from the difference of the percentages of the treatment arm columns.

‡Patients with measurable/evaluable disease.

Table 3. Hematologic toxicities and associated supportive care in patients with advanced ovarian cancer stratified by treatment arm and toxicity grade*

		NCI CTC grade, %												Difference† in the proportions of patients with grades 3/4 toxicity, %	
		TC arm						PT arm							
Toxicity	Set	N	0	1	2	3	4	N	0	1	2	3	4	E	95% CI
Hemoglobin	C	2209	29.1	49.4	20.1	1.3	0.1	2095	33.6	49.5	16.1	0.8	0.0	–0.6	–1.3 to 0.0
	P	388	9.0	40.7	44.3	5.4	0.5	382	14.7	44.2	37.2	3.9	0.0	–2.0	–5.1 to 1.1
Platelets	C	2193	71.9	19.9	5.2	2.5	0.5	2082	93.4	6.2	0.2	0.2	0.0	**–2.9**	**–3.6 to –2.1**
	P	388	43.3	31.2	12.6	10.1	2.8	382	78.3	19.4	1.3	1.0	0.0	**–11.8**	**–15.3 to –8.4**
Transfusion pRBCs‡	C	1868	94.3	—	—	5.7	—	1766	97.2	—	—	2.8	—	**–2.9**	**–4.2 to –1.6**
	P	383	81.7	—	—	18.3	—	370	89.5	—	—	10.5	—	**–7.7**	**–12.7 to –2.8**
Leukocytes	C	2200	37.0	22.6	29.3	10.8	0.3	2073	56.4	23.3	17.3	2.9	0.0	**–8.1**	**–9.6 to –6.6**
	P	388	13.4	16.0	38.7	30.4	1.5	382	31.4	25.1	32.7	10.5	0.3	**–21.2**	**–26.8 to –15.6**
Neutrophils	C	1842	56.9	12.9	12.8	12.4	5.0	1864	70.9	10.6	9.8	6.4	2.3	**–8.7**	**–10.8 to –6.5**
	P	371	31.3	12.9	18.9	21.6	15.4	373	48.0	13.1	16.9	15.0	7.0	**–14.9**	**–21.4 to –8.5**
Febrile neutropenia	C	2228	98.3	—	—	1.7	0.0	2110	99.3	—	—	0.7	0.0	**–0.9**	**–1.6 to –0.3**
	P	388	92.0	—	—	8.0	0.0	384	96.4	—	—	3.6	0.0	**–4.3**	**–7.6 to –1.1**
Supportive care: antibiotics‡	C	1868	98.3	—	—	1.7	—	1768	97.9	—	—	2.1	—	0.4	–0.5 to 1.3
	P	383	93.2	—	—	6.8	—	370	90.5	—	—	9.5	—	2.7	–1.2 to 6.6
Supportive care: G–CSF‡	C	1868	94.0	—	—	6.0	—	1767	98.2	—	—	1.8	—	**–4.2**	**–5.5 to –3.0**
	P	383	85.6	—	—	14.4	—	370	95.4	—	—	4.6	—	**–9.8**	**–13.9 to –5.7**

*TC = paclitaxel/carboplatin combination treatment; PT, cisplatin/paclitaxel combination treatment; NCI CTC = National Cancer Institute (NCI) Common Toxicity Criteria (CTC) *(14,15)*; C = maximum grade over all courses; P = maximum grade over all courses within a patient; N = number of courses in set C and number of patients in set P; E = estimate; CI = confidence interval; pRBCs = packed red blood cells; G–CSF = granulocyte colony-stimulating factor; — = not defined.

†Differences are calculated by subtracting the TC arm proportion from the PT arm proportion; statistically significant differences in proportions between the two treatment arms are bold. All percentages are rounded; therefore, the estimates may differ by ±.1 from the difference of the percentages of the treatment arm columns.

‡Transfusion of pRBCs, use of antibiotics, and G–CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and G–CSF is graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G–CSF is coded as a toxicity of grade 3; a grade 0 is applied otherwise.

Table 4. Non-hematologic toxicities in patients with advanced ovarian cancer stratified by treatment arm and toxicity grade*

		NCI CTC grade, %												Difference† in the proportions of patients with grades 3/4 toxicity, %	
		TC arm						PT arm							
Toxicity	Set	N	0	1	2	3	4	N	0	1	2	3	4	E	95% CI
Ototoxicity	P	388	91.2	3.6	4.9	0.3	0.0	384	83.1	8.1	7.6	1.3	0.0	1.0	–0.2 to 2.3
Hypersensitivity/allergy	P	390	76.4	14.6	5.4	2.6	1.0	384	79.4	11.7	5.5	1.8	1.6	–0.2	–2.8 to 2.4
Cardiac toxicity	P	389	80.7	11.6	4.4	2.8	0.5	384	78.1	12.5	5.2	3.6	0.5	0.8	–1.9 to 3.5
Edema	P	389	81.7	10.8	5.7	1.5	0.3	384	76.6	15.9	7.6	0.0	0.0	**–1.8**	**–3.1 to –0.5**
Alopecia	P	389	1.8	2.6	95.6	—	—	384	1.0	3.6	95.3	—	—	n.d.	n.d.
Constipation/ileus	P	388	50.3	11.6	23.7	13.7	0.8	384	46.9	11.5	27.6	12.8	1.3	–0.4	–5.3 to 4.6
Diarrhea	P	389	75.6	15.4	6.2	1.8	1.0	383	66.8	21.7	8.1	2.3	1.0	0.6	–1.9 to 3.0
Nausea	P	389	22.9	39.8	31.4	5.4	0.5	384	9.1	32.8	43.8	13.8	0.5	**8.4**	**4.2 to 12.6**
Stomatitis/mucositis	P	388	79.6	14.7	5.2	0.5	0.0	384	77.1	18.5	4.2	0.3	0.0	–0.3	–1.1 to 0.6
Vomiting	P	389	54.5	29.0	13.6	2.3	0.5	384	31.5	30.7	27.3	9.1	1.3	**7.6**	**4.1 to 11.1**
Infections	P	388	53.1	5.2	6.2	35.3	0.3	384	55.7	8.9	12.8	22.1	0.5	**–12.9**	**–19.3 to –6.6**
Central neuropathy	P	388	82.5	11.1	4.6	1.5	0.3	384	75.8	14.3	5.7	4.2	0.0	**2.4**	**0.0 to 4.8**
Peripheral sensory neuropathy	P	388	25.0	39.4	28.4	6.7	0.5	384	16.9	33.3	36.2	12.5	1.0	**6.3**	**2.0 to 10.6**
Pain (myalgia/arthralgia)	P	389	28.0	32.4	24.9	12.9	1.8	384	22.9	36.7	29.2	9.6	1.6	–3.5	–8.2 to 1.3
Dyspnea	P	389	72.0	6.9	14.9	4.9	1.3	384	76.6	7.6	11.7	3.1	1.0	–2.0	–5.1 to 1.1
Nephrotoxicity	P	388	94.6	4.6	0.8	0.0	0.0	382	80.01	16.5	3.1	0.0	0.3	0.3	–0.3 to 0.8

*TC = paclitaxel/carboplatin combination treatment; PT = cisplatin/paclitaxel combination treatment; NCI CTC = National Cancer Institute (NCI) Common Toxicity Criteria (CTC) *(14,15)*; P = maximum grade over all courses within a patient; N = number of patients; E = estimate; CI = confidence interval; n.d. = no data for grade 3/4 toxicities; — = not defined.

†Differences are calculated by subtracting the TC arm proportion from the PT arm proportion; statistically significant differences are bold. All percentages are rounded; therefore, the estimates may differ by ±.1 from the difference of the percentages of the treatment arm columns.

treatment did not differ statistically significantly between the two treatment arms.

Non-hematologic toxicities—specifically nausea, vomiting, ototoxicity, renal toxicity, and peripheral sensory neuropathy—were statistically significantly less frequent in the TC arm than in the PT arm (Table 4). The occurrence of alopecia, constipation, diarrhea, mucositis, myalgia/arthralgia, dyspnea, cardial toxicity, edema, and hypersensitivity reactions did not differ statistically significantly between treatment arms. Despite antiemetic prophylaxis consisting of both serotonin type 3 receptor antagonists and corticoids, 69.5% of patients in the PT arm, compared with only 45.5% of patients in the TC arm, experienced at least one treatment cycle with vomiting of any grade. Furthermore, grade 3 nausea was observed in more than twice as many patients in the PT arm than in the TC arm. Renal toxicity and ototoxicity occurred more frequently, albeit not statistically

significantly, in the PT arm than in the TC arm, but they rarely exceeded grades 1 or 2.

Overall, 79.8% of all patients experienced at least grade 1 of some form of neurologic toxicity, which usually consisted of peripheral sensory neuropathy, with motor and central neuropathy occurring in only a few patients. Statistically significantly more patients in the PT arm than patients in the TC arm reported peripheral sensory neurotoxicity (Table 4) of any grade. In addition, treatment-induced neurotoxicity was more severe (grade 3/4 peripheral sensory neurotoxicity: 13.5% in the PT arm versus 7.2% in the TC arm; difference in proportions = 6.3%, 95% CI = 2.0% to 10.6%) and longer lasting (Fig. 2) in patients in the PT arm than it was in patients in the TC arm.

Quality-of-Life Measures

Quality of life was assessed by use of the EORTC QLQ-C30 questionnaire *(18),* which was filled out by each patient at every other treatment cycle, after the last treatment cycle, and 3 and 6 months after cessation of treatment (Fig. 3 and Table 5). At baseline, there were no statistically significant differences in mean quality-of-life scores (52.72 versus 51.11; difference in means = –1.61, 95% CI = –5.15 to 1.93) or any other measured quality-of-life aspect (data not shown) between the two treatment arms. Following the third cycle, mean quality-of-life scores were statistically significantly lower in the PT arm than in the TC arm (57.88 versus 61.55, respectively; difference in means = –3.67, 95% CI = –6.97 to –0.37). Similarly, at the end of treatment, quality-of-life scores were statistically significantly lower in the PT arm than in the TC arm (51.97 versus 65.25; difference in means = –13.28, 95% CI = –18.88 to –7.68). Furthermore, the PT regimen did not show any advantage in any quality-of-life score over the TC regimen at any time point or in any subgroup analysis. Selection bias in these data cannot be excluded because not all patients participated in quality-of-life assessments. However, the intra-individual differences in quality-of-life scores closely matched the differences in quality-of-life scores between treatment arms (Table 5), suggesting a lack of such bias.

Response to Treatment and Survival

The PT regimen was associated with statistically significantly more clinically complete and partial responses (Fig. 1 and Table 2) than the TC regimen (81.4% versus 67.7%, respectively, difference in proportions = 13.7%, 95% CI = 0.9% to 26.4%). However, no statistically significant difference in complete or partial pathologic response was observed between the two treatment regimens at second-look surgery (76.6% in the PT regimen versus 78.4% in the TC regimen; difference in proportions = –1.7%; 95% CI = –15.9% to 12.5%). Approximately half of the patients undergoing second-look surgery exhibited nonevaluable disease or a clinically complete response (36.5% in the TC arm versus 43.3% in the PT arm).

The higher response rates following treatment with the PT regimen did not result in superior progression-free or overall survival (Fig. 4). Median progression-free survival time in the TC arm (17.2 months, 95% CI = 15.2 to 19.3 months) was not statistically significantly different from that in the PT arm (19.1 months, 95% CI = 16.7 to 21.5 months), corresponding to an HR of 1.050 (95% CI = 0.893 to 1.234). Median progression-free survival time was also not statistically significant when the strata were analyzed individually. In stratum 1, median progression-free survival time was 26.0 months (95% CI = 20.5 to 34.8 months) in the TC arm and 24.2 months (95% CI = 21.6 to 29.0 months) in the PT arm, corresponding to an HR of 0.907 (95% CI = 0.718 to 1.147). In stratum 2, median progression-free survival time was 13.4 months (95% CI = 11.9 to 14.9 months) in the TC arm and 14.3 months (95% CI = 12.9 to 16.0 months)

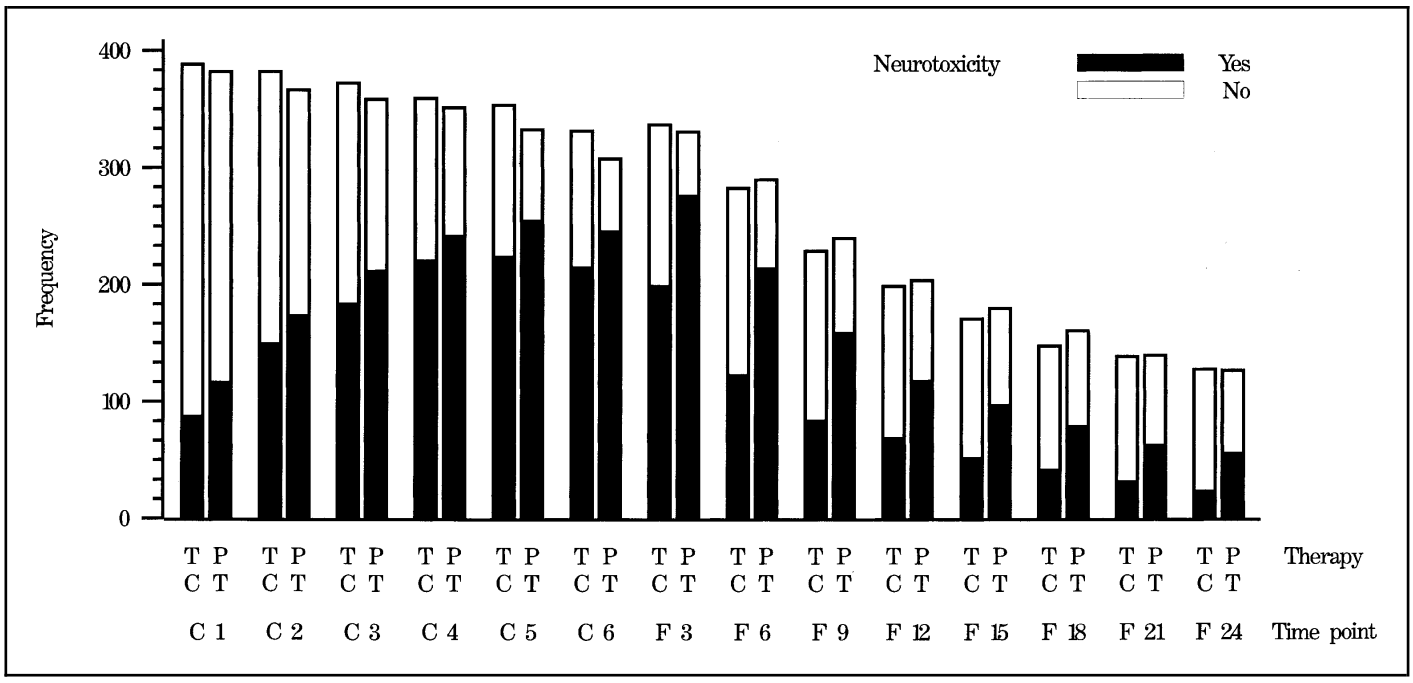

Fig. 2. Neurotoxicity (any grade) during treatment and follow-up. Patients were randomly assigned to receive either paclitaxel-plus-carboplatin combination treatment (TC) or cisplatin-plus-paclitaxel combination treatment (PT). Neurotoxicity, which was measured using the National Cancer Institute Common Toxicity Criteria *(15,16)* at indicated time points, is presented as patients having a neurotoxicity grade (**filled bars**) or not having a neurotoxicity grade (**open bars**). C× = treatment cycle number; F× = follow-up at × months. During follow-up, all observations after the patient's first disease progression were excluded.

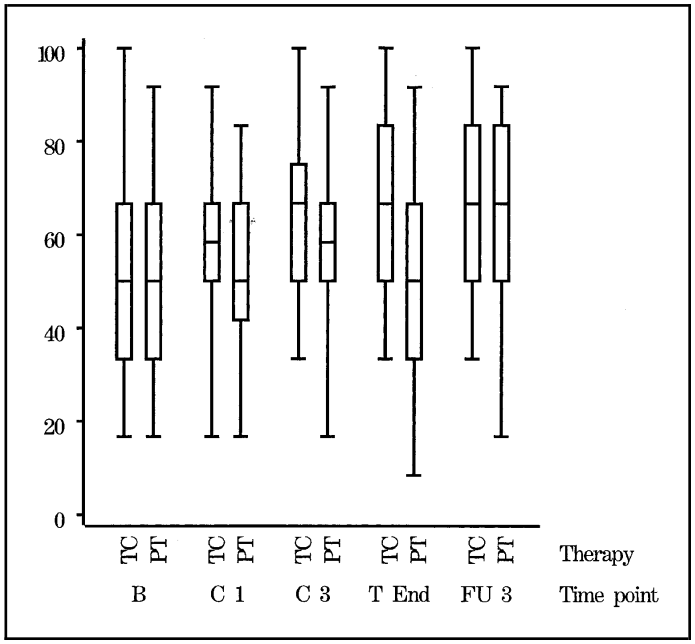

Fig. 3. Global health status/quality-of-life score. Patients were randomly assigned to receive either paclitaxel-plus-carboplatin combination treatment (TC) or cisplatin-plus-paclitaxel combination treatment (PT). Global health status/quality-of-life score was determined using the European Organization for Research and Treatment for Cancer (EORTC) questionnaire QLQ-C30 version 2.0 *(17,18)* at indicated time points. B = baseline; C 1 = after first treatment cycle; C 3 = after third treatment cycle; T End = after cessation of treatment; FU 3 = at 3 months follow-up. **Open rectangles** represent the 1st and 3rd quartiles of the distribution; **cross-lines** represent the median score, and the **whiskers** represent the 2.5th and 97.5th percentile. Descriptive statistics of quality-of-life scores can be seen in Table 5.

in the PT arm, corresponding to an HR of 1.138 (95% CI = 0.908 to 1.426).

Similarly, median overall survival time was not statistically significantly different between the treatment arms (43.3 months, 95% CI = 37.2 to 47.8 months in the TC arm versus 44.1 months, 95% CI = 40.2 to 49.4 months in the PT arm), corresponding to an HR of 1.045 (95% CI = 0.869 to 1.257). Again, when the strata were analyzed individually, no statistically significant difference in overall survival time was observed. In stratum 1, the median overall survival time was 59.4 months (95% CI = 52.3 to 78.8 months) in the TC arm and 55.4 months (95% CI = 48.5 to 72.7 months) in the PT arm, corresponding to an HR of 0.919 (95% CI = 0.695 to 1.216). In stratum 2, the median overall survival time was 31.4 months (95% CI = 27.6 to 36.8 months) in the TC arm and 30.7 months (95% CI = 25.7 to 39.4 months) in the PT arm, corresponding to an HR of 1.081 (95% CI = 0.845 to 1.384).

Patients were followed for a mean of 49.9 months (SD = 13.24 months) in the TC arm and 48.5 months (SD = 14.44 months) in the PT arm. Altogether, 40 patients (5.0%) were lost to follow-up, 29 of whom were lost before disease progression. There were no statistically significant differences in censoring or lost-to-follow-up status between treatment arms (data not shown). Eighteen patients, nine in each treatment arm, developed a secondary malignancy, eight of which were malignancies of the breast. No secondary leukemia was observed.

With respect to the primary endpoint, the difference in the proportion of patients without disease progression at 2 years was not statistically significant between the treatment arms (40.0% for the PT arm versus 37.5% for the TC arm, difference in proportions = 2.5%, two-sided 95% CI = –4.4% to 9.4%, one-sided 95% CI = –∞ to 8.2%; Table 2).

Discussion

This study was designed to test the hypothesis that the tolerability advantage that carboplatin has over cisplatin is maintained when it is combined with paclitaxel without affecting efficacy. The results of the TC regimen were not statistically significantly different from those of the PT regimen in terms of either progression-free or overall survival. The PT regimen was associated with a statistically significantly higher response rate (i.e., complete or partial response) than the TC regimen. However, the results for the response analysis should not be overinterpreted because only a small number of patients had measurable or evaluable disease. Moreover, the study population was not stratified with respect to measurable disease, which may have resulted in imbalances within this small subset of patients. Finally, response to therapy was not assessed or confirmed by independent review *(26)*.

With respect to toxicity, patients in the TC arm suffered more frequently from myelosuppression than patients in the PT arm. However, this side effect was rarely accompanied by clinical

Table 5. Global health status/quality-of-life scores and intra-individual differences in global health scores in patients with advanced ovarian cancer by treatment arm*

	TC arm			PT arm			Total			Difference† in means	
Time point	N	Mean	SD	N	Mean	SD	N	Mean	SD	E	95% CI
Global health status/quality-of-life scores (17,18)											
Baseline	340	52.72	23.76	339	51.11	23.29	679	51.91	23.52	–1.61	–5.15 to 1.93
After 1st treatment cycle	311	58.31	21.11	293	55.72	20.26	604	57.05	20.72	–2.59	–5.89 to 0.71
After 3rd treatment cycle	267	61.55	18.49	258	57.88	20.03	525	59.75	19.33	**–3.67**	**–6.97 to –0.37**
End of treatment	112	65.25	20.41	114	51.97	22.54	226	58.55	22.47	**–13.28**	**–18.88 to –7.68**
3-mo follow-up	271	66.42	21.42	263	58.59	23.08	534	62.56	22.58	**–7.83**	**–11.61 to –4.05**
Intra-individual differences in global health status/quality-of-life scores (i.e., minus baseline)											
After 1st treatment cycle	274	6.4	22.8	264	4.0	21.2	538	5.3	22.1	–2.40	–6.12 to 1.32
After 3rd treatment cycle	234	8.5	23.2	232	5.8	25.5	466	7.2	24.4	–2.70	–7.13 to 1.73
End of treatment	105	12.1	26.0	100	0.4	25.9	205	6.4	26.5	**–11.70**	**–18.80 to –4.60**
3-mo follow-up	237	11.7	25.9	237	4.9	32.1	474	8.3	29.3	**–6.80**	**–12.05 to –1.55**

*E = estimate; SD = standard deviation; CI = confidence interval.

†Differences in means are calculated by subtracting the mean of the TC arm from the mean of the PT arm; statistically significant differences in means are bold.

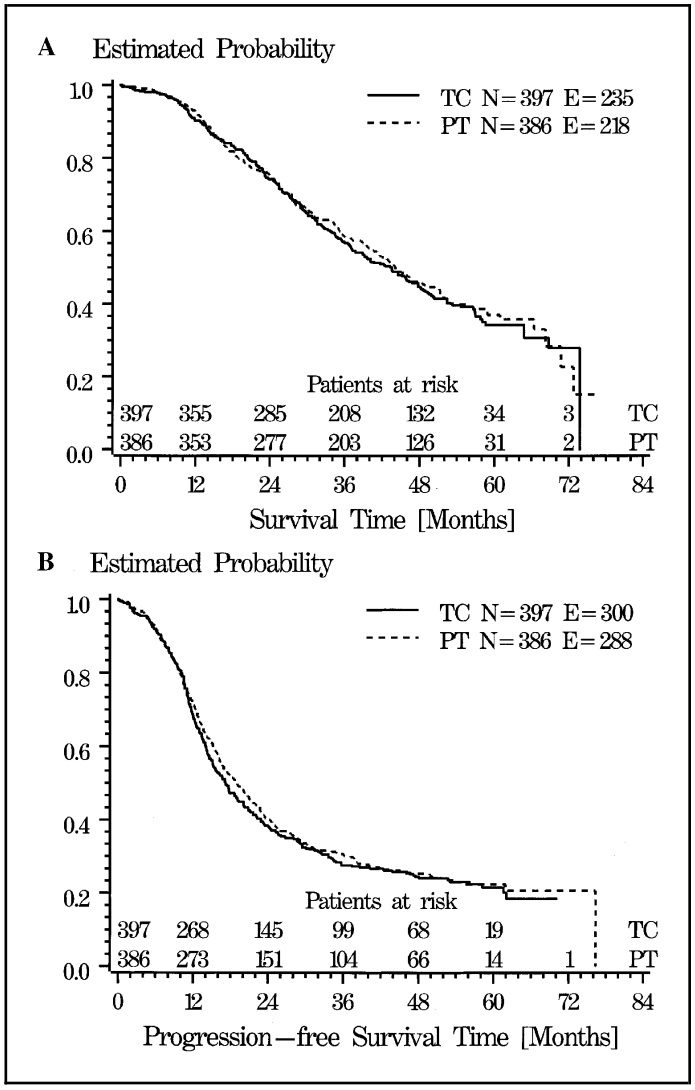

Fig. 4. Kaplan–Meier curves for progression-free and overall survival time in patients with advanced ovarian cancer by treatment arm. Patients were randomly assigned to receive either paclitaxel-plus-carboplatin combination treatment (TC; **solid line**) or cisplatin-plus-paclitaxel combination treatment (PT; **dotted line**). N = number of patients; E = number of events. **A**) Progression-free survival time was not statistically significantly different between the two treatment arms (hazard ratio = 1.050, 95% confidence interval = 0.893 to 1.234). **B**) Overall survival time was also not statistically significantly different between the two treatment arms (hazard ratio = 1.045, 95% confidence interval = 0.869 to 1.257).

symptoms, as indicated by the low rate of febrile neutropenia and non-neutropenic infections. In contrast, patients in the TC arm suffered less frequently from non-hematologic toxicities, such as vomiting and/or nausea or from short- or long-term neuropathy, than patients in the PT arm (Fig. 2). This reduced toxicity in the TC arm was accompanied by an improvement in quality-of-life scores. However, the effect of specific symptoms that only apply to ovarian cancer patients might be underestimated by using generic QLQ instruments. Therefore, the ovarian cancer module of the EORTC QLQ instrument, which was developed after this trial was performed, is now included in all subsequent AGO trials of ovarian cancer.

The results of our study support the findings of other clinical trials *(5,6,27)* of paclitaxel-plus-platinum chemotherapy in patients with ovarian cancer. However, a direct comparison of toxicity outcomes is difficult to perform because of the different grading systems used. Nevertheless, the cisplatin-plus-paclitaxel arm in the study by Piccart et al. *(6),* which also implemented the NCI CTC, showed rates of grade 3/4 gastrointestinal and neurologic toxicities similar to those observed in the PT arm of our study. In a study by Neijt et al. *(27),* which used a different toxicity grading system, changing regimens from PT to TC reduced the incidence of grade 3/4 gastrointestinal and neurologic toxicities 1.2- to 3.0-fold. These findings are similar to our findings that the incidences of grade 3/4 gastrointestinal and neurologic toxicities in the TC arm were reduced 1.4- to 2.7-fold compared with those in the PT arm.

The results for overall and progression-free survival in the PT arm are similar to the findings of three other studies *(5,6,27).* However, the median overall survival times in the PT arm in our study are higher than those in the studies by McGuire et al. *(5),* Piccart et al. *(6),* and Neijt et al. *(27)* (44.1 months versus 38, 35.6, and 30 months, respectively). These differences in overall survival time may reflect the different patient populations in each study. The majority of the patients in our study had a residual tumor size of less than or equal to 1 cm (62.6%), whereas patients with a residual tumor size of less than or equal to 1 cm were in the minority [38.6% *(6)* and 44.4% *(26)*] in the other studies. In addition, all patients in the McGuire et al. study *(5)* had residual tumor sizes of more than 1 cm. In addition, although that study *(5)* included patients with the most unfavorable characteristics with respect to residual tumor, its progression-free and overall survival times were the most similar to our findings. However, it is important to note that the study by McGuire et al. *(5)* was the first trial in which paclitaxel was available to most investigators. Limiting recruitment of patients based on postoperative residual tumor size in a trial that was eagerly awaited by investigators could potentially have biased intra-operative estimation of residual tumors by the surgeons. This problem is even more likely when studying patients with ovarian cancer, because most tumor residuals in these patients are estimated rather than being measured intra-operatively. Therefore, relevant comparisons between the findings of studies in cohorts selected by residual tumor sizes and those of trials, where patients were not excluded based on residual tumor sizes, are difficult.

Our study's more favorable overall survival times as compared with those of the other trials *(6,27)* may reflect different surgical outcomes in different countries, with our study having the lowest proportion of patients with postoperative tumor residuals of more than 1 cm [37.4% versus 55.6% *(6)* and 61.1% *(27)*]. Furthermore, the observed differences in overall survival times between our study and those of others may be due to bias resulting from the proportion of FIGO stage IV patients. Although the proportion of FIGO stage IV patients did not differ substantially between the trials, it was lowest in our study [17.1% versus 18.7% *(6)* and 20.4% *(27)*].

In summary, because the tolerability of the TC regimen was better than that of the PT regimen and treatment efficacy was the same, the substitution of carboplatin for cisplatin in combination with paclitaxel is not only feasible, but may be in the patients' best interest. Hence, the TC combination should be considered an important option for the first-line treatment of patients with advanced ovarian cancer. In addition, the TC combination is a suitable regimen for future research in improving first-line therapy for patients with ovarian cancer. Indeed, the AGO-

OVAR and other study groups within the Gynecologic Cancer Intergroup network have already initiated randomized trials in which the TC combination is compared with a three-drug combination in which anthracyclines [epirubicin *(28,29)* or doxil in GOG trial 182], topotecan [German–French intergroup trial AGO OVAR-7 *(30)*; Canadian–European intergroup trial; GOG 182], or gemcitabine (German–French–Scandinavian intergroup trial; AGO OVAR-9; GOG 182) are added sequentially or concurrently to the carboplatin-plus-paclitaxel combination.

APPENDIX

The following centers recruited four or more patients (in alphabetical order of cities):

K. von Maillot, Aalen; W. Lange, Altenburg; D. Berg, Amberg; E. Schlicht, Aschaffenburg; H. Peterseim, Bad Mergentheim; D. Elling, Berlin; T. Öney, Bremen; V. Zimmermann, Bühl; K. Renziehausen, Chemnitz; G. Rohrmann, Dernbach; H. J. Bach, Dortmund; H. Müller, Erfurt; W. Jäger, Erlangen; H. Mickan, Esslingen; R. H. Ackermann, Flensburg; K. Wernicke, Frankfurt; P. J. Czygan, Frankfurt-Höchst; J. Schulze-Tollert, Freudenstadt; H. J. Becker, Gardelegen; J. Nast, Gehrden; P. Kramb, Gelnhausen; M. Kröner, Gera; E. Petru, Graz; M. Carstensen, Hamburg; W. Müller, Hanau; H. H. Zippel, Hanau; J. Hilfrich, Hannover; W. Herchenhein, Herzberg; M. Mesrogli, Husum; A. Schneider, Jena; G. Deutsch, Karlsruhe; F. K. Klöck, Köln; W. Maurer, Köln; S. Sünter, Köln; A. Göppinger, Lahr; R. Strigl, Landshut; R. Schuhmann, Langen; K. Kühndel, Leipzig; D. Fischer, Lüneburg; C. Leißner, Mainz; F. Peters, Mainz; W. Niedner, Moers; K. H. Peschke, Naumburg; T. Silz, Neubrandenburg; D. Schwörer, Offenburg; W. Meinerz, Paderborn; D. Kramer, Pforzheim; P. Richter, Plauen; D. F. Steichele, Ravensburg; P. Krieger, Reutlingen; M. Lange, Riesa; T. Beck, Rosenheim; K. Friese, D. Rother, Rostock; L. Heilmann, Rüsselsheim; J. Dietel, Schlema; E. Petri, Schwerin; J. Meyer-Grohbrügge, Sigmaringen; V. Jovanovic, Solingen; K. Robke, Steinfurt-Borghorst; E. Merkle, Stuttgart; G. Göretzlehner, Torgau; J. P. Hanker, Trier; C. Karg, Waiblingen; W. Burkert, Walsrode; A. Grüneberger, Wangen; S. Flachsenberg, Wolfsburg.

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NOTES

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