Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

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Purpose: **In randomized trials the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide in advanced-stage epithelial ovarian cancer. Although in nonrandomized trials, carboplatin and paclitaxel was a less toxic and highly active combination regimen, there remained concern regarding its efficacy in patients with small-volume, resected, stage III disease. Thus, we conducted a noninferiority trial of cisplatin and paclitaxel versus carboplatin and paclitaxel in this population.**

Patients and Methods: **Patients with advanced ovarian cancer and no residual mass greater than 1.0 cm after surgery were randomly assigned to receive cisplatin 75 mg/m^2 plus a 24-hour infusion of paclitaxel 135 mg/m^2 (arm I), or carboplatin area under the curve 7.5 intravenously plus paclitaxel 175 mg/m^2 over 3 hours (arm II).**

Results: **Seven hundred ninety-two eligible patients were enrolled onto the study. Prognostic factors were similar in the two treatment groups. Gastrointestinal, renal, and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in arm I. Grade 2 or greater thrombocytopenia was more common in arm II. Neurologic toxicity was similar in both regimens. Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for arm I compared with 20.7 and 57.4 months, respectively, for arm II. The relative risk (RR) of progression for the carboplatin plus paclitaxel group was 0.88 (95% confidence interval [CI], 0.75 to 1.03) and the RR of death was 0.84 (95% CI, 0.70 to 1.02).**

Conclusion: **In patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior, when compared with cisplatin plus paclitaxel.**

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IN THE United States, standard therapy for women with advanced epithelial ovarian cancer has developed from a series of randomized trials performed primarily by the Gynecologic Oncology Group (GOG). In 1996, this group reported the results of a randomized comparison of cisplatin and cyclophosphamide versus cisplatin and paclitaxel in patients with previously untreated advanced stage III and IV disease.[1] The cisplatin plus paclitaxel regimen was judged superior on the basis of the following results of that trial: an overall improved response rate (73% *v* 60%; $P = .01$); an increased clinical complete response rate (54% *v* 32%); an increase in progression-free survival (PFS; 18.1 *v* 13.6 months; $P < .001$); and, most importantly, an increased overall median survival (38 *v* 24 months; $P < .001$). The results of this study were subsequently confirmed by a European-Canadian trial in patients with stage IIB through IV epithelial ovarian cancer who were similarly randomly assigned to a cisplatin plus cyclophosphamide regimen versus cisplatin plus paclitaxel.[2] In the latter study, cisplatin was combined with paclitaxel administered as a 3-hour infusion, whereas in the GOG trial, paclitaxel was administered as a 24-hour infusion. Furthermore, in the GOG protocol, only suboptimal stage III and IV patients were included (residual masses > 1.0 cm after initial surgery) and there was minimal cross-over to paclitaxel in patients who were initially randomly assigned to receive cisplatin plus cyclophosphamide. Despite these differences in protocol design, both studies demonstrated superiority of initial treatment with cisplatin plus paclitaxel in patients with previously untreated advanced ovarian cancer.

Carboplatin, an analog of cisplatin, has less nonhematologic toxicity than the parent compound. Most randomized trials have reported comparable activity between cisplatin and carboplatin

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in previously untreated patients with advanced ovarian cancer.[3,4] However, some investigators questioned whether this analog demonstrated equal efficacy in patients with small-volume stage III disease (no tumor nodule > 1.0 cm after initial surgery). An International Ovarian Cancer Consensus Conference in 1993 recommended that carboplatin should not routinely replace cisplatin in patients with potentially curable small-volume stage III disease.[5]

On the basis of these considerations, a phase I study combining carboplatin and paclitaxel was conducted in patients with previously untreated advanced-stage ovarian cancer.[6] Initially, cohorts of patients received paclitaxel at 135 mg/m^2 as a 24-hour infusion, with individual groups of patients receiving carboplatin escalated from an area under the curve (AUC) of 5.0 to 7.5 to 10.0 mg/mL/min. The maximum-tolerated dose was determined to be paclitaxel 135 mg/m^2 in a 24-hour infusion followed by carboplatin at an AUC of 7.5. With multiple cycles of treatment, cumulative granulocytopenia developed and most patients required the addition of colony-stimulating factors (G-CSF) to maintain dose. This phase I study was subsequently amended on the basis of results of a European-Canadian trial that compared 3- *v* 24-hour infusions of paclitaxel.[7] In that trial, patients with recurrent ovarian cancer (previously untreated for recurrence) were randomly assigned in a 2 × 2 factorial trial design to receive either a 3- or 24-hour infusion of paclitaxel at a dose of either 135 or 175 mg/m^2. This trial demonstrated that paclitaxel could safely be administered in a 3-hour schedule with premedication, and that there was significantly less myelosuppression with 3- *v* 24-hour infusion. Furthermore, the efficacy of the 3-hour infusion was comparable to that observed with the 24-hour infusion.[7]

Consequently, in the GOG pilot protocol, additional groups of patients received carboplatin at an AUC of 7.5 in combination with a 3-hour paclitaxel infusion that was escalated from 175 to 225 mg/m^2.[6] In this phase I trial, paclitaxel 175 mg/m^2 over 3 hours followed by carboplatin at an AUC of 7.5 over 30 minutes was identified as the dose and schedule for phase II and phase III trials on the basis of acceptable hematologic toxicity without the need for G-CSF. At this dose level, there were no hospitalizations for febrile neutropenia and no platelet transfusions were required. With the exception of paclitaxel-induced alopecia, there was minimal nonhematologic toxicity reported. Peripheral neuropathy was uncommon and did not exceed grade 2. The most common toxicity was nausea and vomiting, which was easily managed with antiemetics.

The combination of carboplatin plus paclitaxel was found to be an active regimen. In 24 patients with measurable disease, the overall response rate was 75%, including complete responses in 67% of patients. On the basis of the results of the pilot study, GOG Protocol 158 was designed as a noninferiority study to compare the efficacy and toxicity of carboplatin plus paclitaxel with cisplatin plus paclitaxel, which at that time, was the GOG standard treatment regimen for patients with small-volume stage III disease.

PATIENTS AND METHODS

Women with pathologically verified stage III epithelial ovarian cancer (borderline tumors were excluded) underwent a staging laparotomy with cytoreduction. Those who were left with no residual disease greater than 1.0 cm in diameter were eligible for the study. Eligibility criteria also included no previous chemotherapy, a GOG performance status of 0 to 2, WBC at least 3,000/μL, platelets at least 100,000/μL, serum creatinine 2.0 mg/dL or less, and serum bilirubin and AST values of no more than 2 × the institutional upper level of normal. Patients provided written informed consent consistent with all federal, state, and local requirements and must have entered onto the study within 6 weeks of laparotomy. They could not have had previous chemotherapy or radiation for ovarian cancer, nor any previous cancer other than nonmelanoma skin cancer. Pathologic material was centrally reviewed by the GOG Pathology Committee. Each patient case was also reviewed for adequacy of initial surgical procedure, and all of the operative and pathology reports were reviewed to verify eligibility.

On study entry, patients underwent a history, physical examination, and laboratory procedures. Because eligibility disallowed tumor nodules more than 1.0 cm after the initial laparotomy, imaging procedures were not required until completion of six cycles of therapy.

Women in the standard therapy group were to receive cisplatin 75 mg/m^2 intravenously at 1 mg/min and paclitaxel 135 mg/m^2 intravenously as a 24-hour continuous infusion every 3 weeks for a total of six courses. Patients in the experimental group received carboplatin at an AUC of 7.5 mg/mL/min and paclitaxel 175 mg/m^2 as a 3-hour infusion. The carboplatin dose in milligrams was based on the Calvert formula[8]: dose in milligrams = target AUC × [glomerular filtration rate (GFR) + 25]. Creatinine clearance was substituted for GFR and was calculated using the Jelliffe[9] formula on the basis of the patient's weight, age, and serum creatinine level. Premedication consisted of dexamethasone 20 mg orally 12 and 6 hours before the infusion or 20 mg intravenously 30 minutes before the paclitaxel infusion.[10] Both diphenhydramine 50 mg and cimetidine 300 mg were administered intravenously 30 minutes before the paclitaxel infusion.

Adverse effects were graded according to standard GOG toxicity criteria. Patients must have had an absolute neutrophil count ≥ 1,000/μL and platelets more than 100,000/μL before receiving the next course of therapy. Treatment modifications included cycle delay, dose reduction, and the addition of G-CSF (in that sequence). There was no dose modification for uncomplicated nadirs. Patients who required a delay of 2 weeks or less received no dose modification from the previous cycle and G-CSF was not instituted. Those who required a delay of greater than 2 but no more than 3 weeks received modified doses. If patients in the latter group experienced recurrent delays of more than 2 weeks or developed febrile neutropenia during subsequent cycles, G-CSF was added at a dose of 5 μg/kg/d beginning 24 hours after the completion of chemotherapy and continuing for 14 days without further modification to chemotherapy doses. Cycles were not delayed for any gastrointestinal toxicity, grade 1 to 2 peripheral neuropathy, or mild renal toxicity (serum creatinine ≤ 2 mg/dL or creatinine clearance ≥ 50 mL/min). More severe neurologic or renal toxicity that had not resolved before the next scheduled dose necessitated discontinuation of protocol therapy, but follow-up was continued.

At the time of random assignment to treatment arm, the decision to undergo or not undergo second-look laparotomy at the completion of chemotherapy (provided patients met the criteria for surgery) was made. In women who underwent reassessment laparotomy, pathologic response was determined and defined according to one of the following three categories: complete response, partial response with microscopic disease only, or persistent disease.

The GOG Statistical and Data Center randomly assigned the treatment regimen employing a fixed block with an equal number of each regimen after stratification on the amount of residual disease (microscopic or macroscopic) after initial laparotomy and the option of whether a second-look laparotomy was planned after treatment was completed. A sample size of 720 patients was set, with an estimated 3 years (6 years for survival) of follow-up, to observe 382 recurrences (382 deaths for survival) before testing the noninferiority hypothesis: Does carboplatin plus paclitaxel decrease recurrence-

Table 1. Patient Characteristics

Characteristic	Cisplatin + Paclitaxel (n = 400)		Carboplatin + Paclitaxel (n = 392)	
	No. of Patients	%	No. of Patients	%
Age, years				
21-30	2	1	5	1
31-40	28	7	26	7
41-50	101	25	83	21
51-60	109	27	128	33
61-70	117	29	98	25
71-80	38	10	47	12
81-90	5	1	5	1
Ethnicity				
White	353	88	328	84
Black	25	6	25	6
Hispanic	13	3	27	7
Other	9	2	12	3
GOG performance status				
0	182	46	169	43
1	188	47	192	49
2	30	8	31	8
Cell type				
Serous adenocarcinoma	281	70	290	74
Endometrioid adenocarcinoma	45	11	35	9
Mucinous adenocarcinoma	10	3	9	2
Clear-cell carcinoma	10	3	21	5
Other	54	14	37	9
Tumor grade				
1	44	11	35	9
2	139	35	141	36
3	217	54	216	55
Residual disease				
None or microscopic	144	36	137	35
Gross	256	64	255	65
Optional second-look laparotomy				
Yes	201	50	192	49
No	199	50	200	51

Abbreviation: GOG, Gynecologic Oncology Group.

free survival when compared with cisplatin plus paclitaxel in patients with small-volume stage III ovarian cancer? This was a one-sided test with the probability of a type I and type II error both set at .1 for a hazard ratio (carboplatin plus paclitaxel compared with cisplatin plus paclitaxel) of 1.3. These operating characteristics were selected because of the importance of detecting a moderate-sized loss in efficacy with the use of carboplatin plus paclitaxel. A hazard ratio of 1.25 would be detectable with 80% power given the sample size goal.

Overall survival (OS) and PFS were measured from the date of random assignment to treatment. The duration of OS was measured up to the date of death or, for patients still alive, the date of last contact. The duration of PFS was the minimum amount of time until clinical progression, death, or date of last contact. All eligible patients were included in the analysis of OS and PFS (intent-to-treat principle for eligible patients). All causes of death were used to calculate survival, and the estimates of the cumulative proportions of survival were based on Kaplan-Meier procedures.[11] Relative risk (RR) estimates and confidence intervals (CIs) of treatment effects on failure and death while adjusting for prognostic factors was accomplished using the Cox model.[12]

Only eligible women who received at least one course of treatment were included in the assessment of toxicity. The Kruskal-Wallis rank test adjusted for ties was used to test the independence of severity of toxicity (grade 0 to 4) to the assigned treatment.[13]

RESULTS

Eight hundred forty patients entered onto the trial. Forty-eight women, equally distributed between the two treatment groups, were deemed ineligible for the following reasons: wrong stage (14 patients); borderline tumor or not invasive carcinoma (11 patients); inadequate surgery (10 patients); and various pathologic exclusions (eg, wrong cell type) on central pathology review (13 patients). The remaining 792 eligible patients with small-volume stage III disease were randomly assigned to either cisplatin plus paclitaxel or to carboplatin plus paclitaxel. The two groups were balanced for several prognostic factors (Table 1). Slightly more nonwhite (16% *v*

Table 2. Maximum Chemotherapy Cycles Received

Cycle	Cisplatin + Paclitaxel (n = 400)*		Carboplatin + Paclitaxel (n = 392)*	
	No. of Patients	%	No. of Patients	%
1	13	3	11	3
2	8	2	11	3
3	14	4	7	2
4	5	1	11	3
5	17	4	9	2
6	341	85	342	87

*Three patients (two patients from cisplatin + paclitaxel group and one patient from carboplatin + paclitaxel group) did not receive any protocol therapy.

Table 3. Average Dose per Cycle of Chemotherapy

Drug	Cisplatin + Paclitaxel 24-Hour Infusion			Carboplatin + Paclitaxel 3-Hour Infusion		
	Median	10th P	90th P	Median	10th P	90th P
Cisplatin, mg/m^2	74.1	54.7	75.9	—	—	—
Paclitaxel, mg/m^2	133.2	114.2	136.4	174.8	164.5	178.1
Carboplatin, AUC	—	—	—	7.43	5.83	7.65

Abbreviations: AUC, area under the curve; P, percentile.

12%) and patients with serous adenocarcinomas tumors (74% *v* 70%) were randomly assigned to the carboplatin plus paclitaxel group. Sixty-five percent of patients had gross residual disease, whereas the remaining patients had no residual or microscopic disease after the initial laparotomy.

Table 2 summarizes the number of cycles by treatment and Table 3 summarizes the average dose of chemotherapy received per cycle. Eighty-five percent of patients completed six cycles of the cisplatin regimen compared with 87% of those completing the carboplatin regimen. In patients randomly assigned to arm I, the median (average dose per cycle) dose of cisplatin and paclitaxel was 74.1 and 133 mg/m^2, respectively. Among patients randomly assigned to carboplatin and paclitaxel, the median AUC was 7.4 and dose was 175 mg/m^2, respectively.

Grade 3 to 4 adverse effects are listed in Table 4. Patients treated with the cisplatin regimen experienced more (statistically significant) leukopenia, gastrointestinal, renal (genitourinary), and metabolic (hypomagnesemia or abnormal electrolytes) toxicities than did those treated with carboplatin. Patients treated with the carboplatin regimen experienced more (statistically significant) grade 2 to 4 thrombocytopenia and grade 1 to 2 pain. Grade 3 or 4 neutropenia occurred in the majority of women on this trial, but its consequences were manageable, with few patients having documented infection or requiring hospitalization. Regarding thrombocytopenia, there were no reports of clinically significant bleeding or the need for platelet transfusion. Grade 2 to 4 neurologic toxicity (primarily peripheral neuropathy) occurred with similar frequency; 31% in the cisplatin arm and 28% in the carboplatin arm.

Inasmuch as the protocol included only patients with small-volume stage III disease, eligible patients did not have measurable disease. A second-look laparotomy to assess disease status after six cycles of chemotherapy was not mandatory, and surgically confirmed negative second-look frequency was not a statistical end point of this study. However, it was required that the decision regarding whether a patient would undergo second-look laparotomy after six cycles of chemotherapy be made at the time of registration. Three hundred ninety-three (50%) patients elected second-look surgery and results are summarized in Table 5. Of the 325 patients who either underwent surgical restaging or had clinically determined progressive disease before the restaging procedure could be performed, there were 160 (50%) negative second-look laparotomies.

Two hundred eighty-five (73%) patients treated with carboplatin and paclitaxel have experienced a recurrence of disease compared with 303 (76%) treated with cisplatin and paclitaxel. Figure 1 displays PFS, which includes 25 deaths that occurred without prior documented recurrence. Ninety percent of patients have been observed for at least 48 months or have died. Median PFS in the carboplatin group is 20.7 months compared with 19.4 months for the cisplatin group (not significant). The RR of treatment failure is 0.88 (95% CI, 0.75 to 1.03) when comparing carboplatin plus paclitaxel with cisplatin plus paclitaxel. Figure 2 compares the PFS by treatment group stratified by whether the patient had any gross residual disease after surgery. The RR of treatment failure for carboplatin plus paclitaxel to cisplatin plus paclitaxel is 0.89 and 0.85 in patients with gross residual disease and those with microscopic or no residual disease, respectively.

Two hundred seven patients (53%) treated with carboplatin plus paclitaxel have died compared with 230 patients (58%) treated with cisplatin plus paclitaxel. Median survival is 57.4 months for carboplatin plus paclitaxel versus 48.7 months for

Table 4. Grade 3 to 4 Adverse Effects

Adverse Effect	Cisplatin + Paclitaxel (n = 400)				Carboplatin + Paclitaxel (n = 392)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia*	205	51	49	12	207	53	23	6
Thrombocytopenia*	11	3	9	2	74	19	80	20
Granulocytopenia	60	15	312	78	67	17	284	72
Gastrointestinal*	55	14	35	9	20	5	19	5
Neurologic	30	8	1	0	26	7	1	0
Alopecia	0	0	0	0	0	0	0	0
Metabolic*	24	6	7	2	6	2	3	1
Genitourinary*	11	3	1	0	3	1	0	0
Pain*†	2	1	1	0	2	1	1	0

*Statistically significant difference at the .05 level.

†Grade 1 to 2 pain: carboplatin + paclitaxel = 101 (26%); cisplatin + paclitaxel = 60 (15%).

Table 5. Second-Look Laparotomy Results

Finding at Second Look	Cisplatin + Paclitaxel		Carboplatin + Paclitaxel	
	No. of Patients	%	No. of Patients	%
Negative second look	77	46	83	53
Positive second look	76	45	58	37
Early clinical progression or death	15	9	16	10
Total with known outcome	168	100	157	100
Results not available				
Refused surgery	28*		31*	
Surgery medically contraindicated	5		4	
Total not available	33		35	

*Overall frequency of refusal is 15%.

cisplatin plus paclitaxel (Fig 3). The RR is 0.84 (95% CI, 0.70 to 1.02). Figure 4 compares survival between patients with macroscopic residual disease and patients with no (or microscopic) disease by treatment group. The RR estimates for treatment within the residual disease categories are the same.

Figure 5 compares survival from time of recurrence by treatment. Median survival after recurrence is 23 months, and in this exploratory subset analysis there does not appear to be any difference between treatments. Recurrence is associated with a poor prognosis and long-term survival ($>$ 60 months) is infrequent, without any evidence for a plateau.

DISCUSSION

The results of this study demonstrate that the combination of carboplatin plus paclitaxel is not inferior to cisplatin plus paclitaxel with regard to PFS and survival in patients with small-volume stage III epithelial ovarian cancer. The RR of failure is 0.88 (95% CI, 0.75 to 1.03). The RR of death is 0.84 (95% CI, 0.70 to 1.02). This study was designed as a noninferiority trial and the results essentially exclude the possibility that the carboplatin regimen is inferior to the cisplatin regimen. This trial was not designed to determine whether the carboplatin regimen was superior to the cisplatin regimen. Nonetheless, the 16% reduced risk of death is of interest because it is suggestive that carboplatin may provide a slight increase in efficacy over cisplatin. The dose of carboplatin (AUC 7.5) in this trial may result in more platinum exposure than the cisplatin dose (75 mg/m^2). However, previous trials have failed to show a benefit for increasing doses of carboplatin (either as a single agent or in combination with cyclophosphamide).[14,15] It is possible that a pharmacodynamic interaction exists between carboplatin plus paclitaxel, resulting in a better outcome when higher doses of carboplatin are used in combination with paclitaxel.

It is unlikely that a 3-hour infusion of paclitaxel (as used in combination with carboplatin) is superior to a 24-hour infusion (as used in combination with cisplatin) because previous randomized trials have not demonstrated a significant difference in outcomes with different schedules of administration.[7] However, to identify the potential role of carboplatin AUC 7.5 versus any lower dose of carboplatin would require a prospective randomized trial that compares two different doses of carboplatin in combination with the same dose and schedule of paclitaxel.

Two other prospective randomized trials have been performed comparing carboplatin plus paclitaxel versus cisplatin plus paclitaxel in patients with advanced ovarian cancer. In the Danish-Netherlands Trial,[16] there was an insufficient number of patients to determine a statistical equivalency, whereas in the Arbeitsgemeinschaft Gynäkologie trial from Germany,[17] 800 patients with

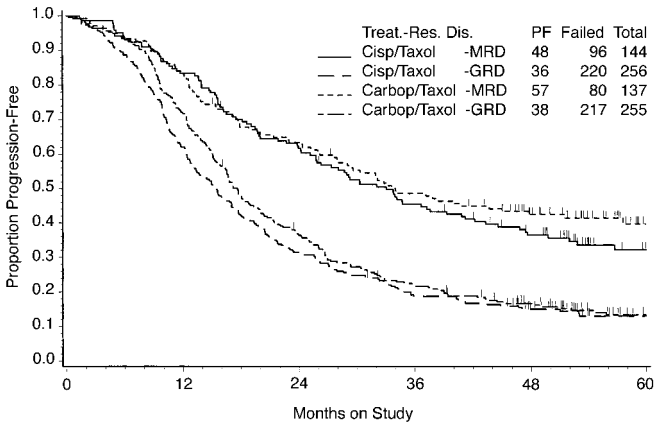

Fig 2. Progression-free survival by treatment group and microscopic (Micro) or gross residual disease (Res. Dis.). Treat., treatment; Carbop, carboplatin; Cisp, cisplatin.

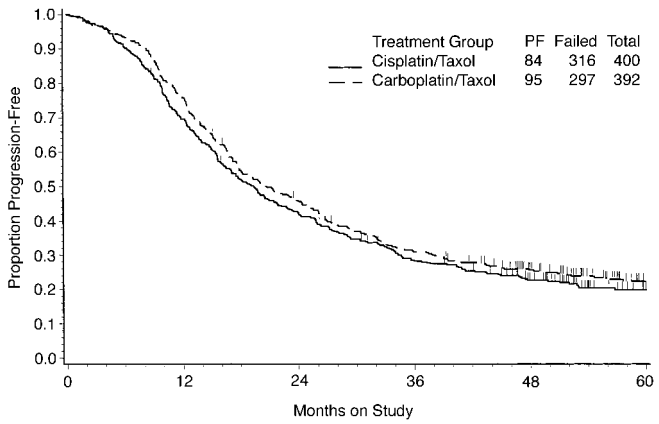

Fig 1. Progression-free survival by treatment group.

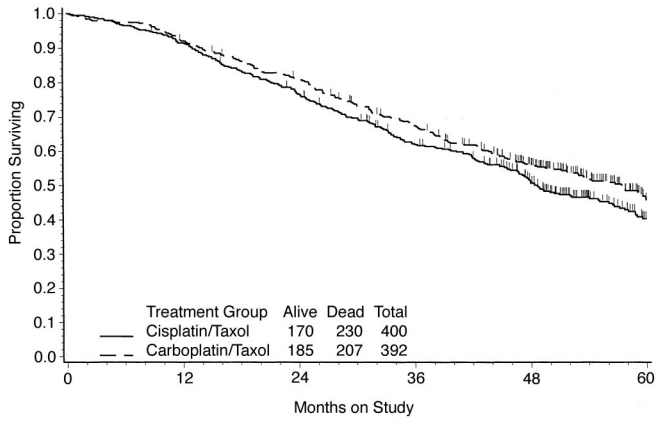

Fig 3. Observed survival by treatment group.

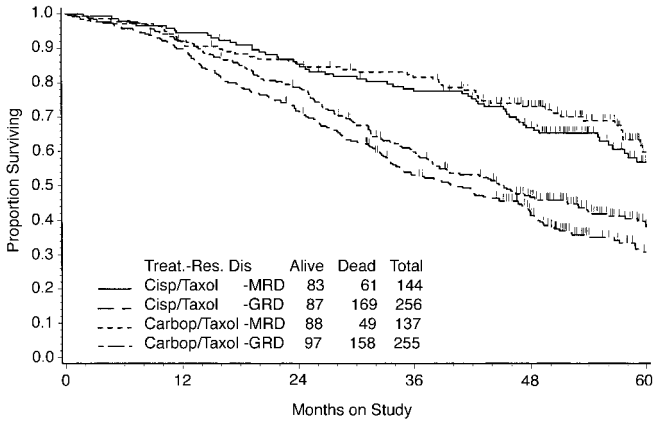

Fig 4. Observed survival by treatment group, and microscopic (Micro) or gross residual disease (Res. Dis.). Treat., treatment; Carbop, carboplatin; Cisp, cisplatin.

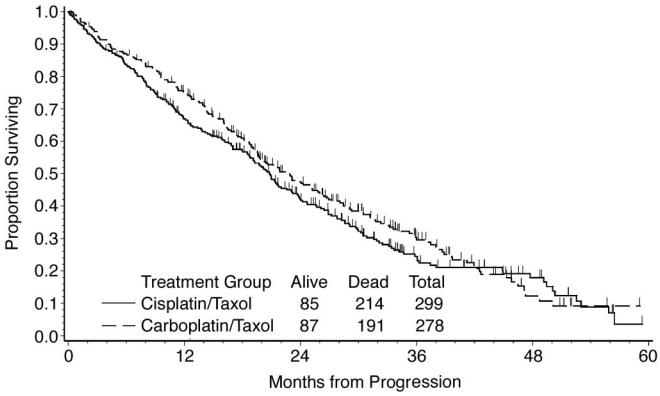

Fig 5. Survival from time of recurrence by treatment group.

advanced-stage ovarian cancer were randomly assigned to similar regimens. Investigators reported no significant difference in PFS and OS between the two treatment groups. However, in the German study, the cisplatin plus paclitaxel regimen used paclitaxel 185 mg/m^2 as a 3-hour infusion instead of 135 mg/m^2 as a 24-hour infusion as used by the GOG in its combination trial with cisplatin. In addition, the carboplatin plus paclitaxel regimen used a slightly lower dose of carboplatin (AUC 6.0 versus 7.5) and a higher dose of 3-hour paclitaxel (185 instead of 175 mg/m^2). Both European trials included patients with stage II to IV disease.

In contrast, GOG Protocol 158 was confined to patients with small-volume stage III disease, and it is within this group of patients that a decrease in efficacy could have the greatest potential influence on survival. The GOG trial fails to support the hypothesis that carboplatin is inferior to cisplatin in patients with small-volume stage III ovarian cancer. Similarly, concerns had been raised regarding the relative efficacy of a 3-hour infusion of paclitaxel versus prolonged infusions[1] on the basis of in vitro toxicity data that demonstrated increased cell kill with prolonged exposure to paclitaxel.[18] The results of this trial, however, failed to support the contention that a 3-hour infusion is less efficacious than a 24-hour infusion of paclitaxel in patients with small-volume stage III ovarian cancer when used in combination with a platinum compound.

The carboplatin plus paclitaxel regimen was also associated with less gastrointestinal and metabolic toxicity (Table 4). The difference in toxicity relates primarily to increased nephrotoxicity caused by cisplatin and to its emetogenic effects. Of note in this study is that there was no difference reported for neurotoxicity at the completion of six cycles of treatment. Both European studies[16,17] have reported less neurotoxicity with the carboplatin plus paclitaxel regimen when compared with cisplatin plus paclitaxel. However, in those studies, cisplatin was combined with a 3-hour infusion of paclitaxel, which is a schedule that shows a high degree of neurotoxicity.[2] Furthermore, the outpatient carboplatin plus paclitaxel regimen is easier to administer than is the cisplatin plus paclitaxel regimen, for which most patients are hospitalized for a 24-hour paclitaxel infusion. On the basis of at least equal activity with regard to PFS and OS, and a more favorable toxicity profile, carboplatin plus paclitaxel is considered the preferred regimen for patients with small-volume stage III ovarian cancer.

Although this study has demonstrated that carboplatin plus paclitaxel is the current treatment of choice for patients with small-volume stage III disease, the results also emphasize the need for more effective therapy. More than 70% of patients have experienced disease recurrence, with a median time to progression of less than 2 years. Median survival after progression is less than 2 years, and median survival from time of diagnosis is between 4 and 5 years. This indicates that treatment after progression, although not curative, may extend survival.

The GOG, in cooperation with investigators from Europe and Asia, is performing a five-arm randomized trial comparing carboplatin plus paclitaxel to new three-drug combinations (carboplatin plus paclitaxel plus gemcitabine, or carboplatin plus paclitaxel plus encapsulated doxorubicin) and sequential doublets (carboplatin and topotecan followed by carboplatin and paclitaxel, or carboplatin and gemcitabine followed by carboplatin and paclitaxel).[19] Until that trial is completed, the standard therapy for ovarian cancer in the GOG continues to be the two-drug combination of carboplatin plus paclitaxel.

APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

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