ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

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ABSTRACT

BACKGROUND

Standard chemotherapy for newly diagnosed ovarian cancer is a platinum–taxane combination. The Gynecologic Oncology Group conducted a randomized, phase 3 trial that compared intravenous paclitaxel plus cisplatin with intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel in patients with stage III ovarian cancer.

METHODS

We randomly assigned patients with stage III ovarian carcinoma or primary peritoneal carcinoma with no residual mass greater than 1.0 cm to receive 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period followed by either 75 mg of intravenous cisplatin per square meter on day 2 (intravenous-therapy group) or 100 mg of intraperitoneal cisplatin per square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 (intraperitoneal-therapy group). Treatment was given every three weeks for six cycles. Quality of life was assessed.

RESULTS

Of 429 patients who underwent randomization, 415 were eligible. Grade 3 and 4 pain, fatigue, and hematologic, gastrointestinal, metabolic, and neurologic toxic effects were more common in the intraperitoneal-therapy group than in the intravenous-therapy group ($P \leq 0.001$). Only 42 percent of the patients in the intraperitoneal-therapy group completed six cycles of the assigned therapy, but the median duration of progression-free survival in the intravenous-therapy and intraperitoneal-therapy groups was 18.3 and 23.8 months, respectively ($P=0.05$ by the log-rank test). The median duration of overall survival in the intravenous-therapy and intraperitoneal-therapy groups was 49.7 and 65.6 months, respectively ($P=0.03$ by the log-rank test). Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to six weeks after treatment but not one year after treatment.

CONCLUSIONS

As compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer.

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Ovarian cancer is the leading cause of death from a gynecologic cancer in the United States.[1] In most cases, the high death rate is due to tumor that has spread beyond the ovary at the time of diagnosis.[2] In the United States, the standard chemotherapy for the initial treatment of ovarian cancer is a combination of a platinum analogue with paclitaxel.[3,4] With modern surgical interventions and contemporary chemotherapy, most patients attain complete clinical remission.[3,5] The majority of them, however, will eventually have a relapse and die of the disease.

The peritoneal cavity is the principal site of disease in ovarian cancer.[2,6] Although the intensity of intravenous chemotherapy is limited mainly by myelotoxicity, several active drugs can be administered directly into the peritoneal cavity. The rationale for intraperitoneal therapy in ovarian cancer is that the peritoneum, the predominant site of tumor, receives sustained exposure to high concentrations of antitumor agents while normal tissues, such as the bone marrow, are relatively spared.

Two randomized, phase 3 intergroup trials have compared intraperitoneal with intravenous chemotherapy in advanced, low-volume ovarian cancer.[7,8] The first demonstrated a statistically significant survival advantage among patients treated with intraperitoneal chemotherapy, but the regimen did not include paclitaxel.[7] The second trial showed a significant difference in progression-free survival, but the difference in overall survival was of borderline significance (P=0.05). Furthermore, the intraperitoneal-therapy group included two cycles of moderately intensive intravenous carboplatin, which complicated the interpretation of results and added to the toxicity of the treatment.[8] Neither of these trials led to widespread acceptance of intraperitoneal treatment. The reluctance of clinicians to embrace intraperitoneal therapy is due to multiple factors, including its high cost and toxicity and clinicians' lack of familiarity with peritoneal administration and catheter-placement techniques. The possibility that improved outcomes with newer forms of therapy could replace intraperitoneal treatment has also been a consideration.[9,10]

We report the results of a randomized, phase 3 trial in which a regimen of six cycles of treatment with intravenous paclitaxel followed by intravenous cisplatin was compared with six cycles of intravenous paclitaxel followed by intraperitoneal cisplatin and intraperitoneal paclitaxel in women with previously untreated stage III ovarian cancer.

METHODS

PATIENTS

Eligible patients had stage III epithelial ovarian or peritoneal carcinoma with no residual mass greater than 1.0 cm in diameter after surgery, a Gynecologic Oncology Group (GOG) performance status of 0 to 2 (with 0 being fully active and 4 completely disabled), normal blood counts, and adequate renal and hepatic function. All cases were centrally reviewed by the GOG to confirm patients' surgical and pathological eligibility for enrollment. This review was not strictly blinded. However, pathology reports, operative notes, and eligibility information were collected before registration. Patients who had undergone prior chemotherapy or radiation for ovarian cancer were not eligible. All patients gave written informed consent according to institutional and federal guidelines before enrollment. Approval was granted by the institutional review board at each participating site.

At registration, participants decided whether they would undergo a second-look laparotomy at the completion of chemotherapy. At study entry and before each treatment, a physical examination was performed and medical history taking, complete blood count, blood chemical measurements, and measurement of serum ovarian cancer antigen 125 were carried out. This evaluation was repeated at the completion of therapy, every 3 months for 24 months, and then every 6 months. Quality-of-life assessment, with use of the Functional Assessment of Cancer Therapy — Ovarian (FACT-O) instrument,[11] was performed four times: at registration, before cycle 4, 3 to 6 weeks after cycle 6, and 12 months after the completion of therapy. All patients were followed for clinical progression and death.

TREATMENT PLAN

Patients were randomly assigned to receive either 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period on day 1 followed by 75 mg of intravenous cisplatin per square meter on day 2 (intravenous-therapy group) or 135 mg of intravenous paclitaxel per square meter over a 24-hour period on day 1 followed by 100 mg of intraperitoneal cisplatin per

square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 (intraperitoneal-therapy group). Standard premedication was given to prevent hypersensitivity reactions to paclitaxel. Hydration and antiemetic agents were given before cisplatin was administered. For intraperitoneal therapy, paclitaxel or cisplatin was reconstituted in 2 liters of warmed normal saline and infused as rapidly as possible through an implantable peritoneal catheter. Treatments were administered every three weeks for six cycles.

Before they could receive a subsequent cycle of therapy, patients were required to have an absolute neutrophil count of 1500 cells per cubic millimeter or greater, a platelet count of 100,000 cells per cubic millimeter or greater, and a creatinine level of 2.0 mg per deciliter or less. Treatment modifications for hematologic toxic effects included cycle delay, dose reduction, and the addition of granulocyte colony-stimulating factor (in that sequence). There was no dose modification if the nadir of leukopenia was not accompanied by fever. Treatment was postponed in the case of grade 3 or 4 peripheral neuropathy, a creatinine level greater than 2.0 mg per deciliter, or a creatinine clearance of less than 50 ml per minute. Patients in whom treatment was delayed for more than three weeks were removed from the study.

Among patients in the intraperitoneal-therapy group, the dose of intraperitoneal drug was reduced if there was grade 2 abdominal pain. Patients with grade 3 abdominal pain, recurrent grade 2 abdominal pain after a dose reduction, or complications involving the intraperitoneal catheter that prohibited further intraperitoneal therapy received intravenous chemotherapy for the remaining cycles. The dose of cisplatin was reduced if there was grade 2 peripheral neuropathy. Women in either group who had a cisplatin-related toxic effect requiring discontinuation of the protocol treatment received intravenous therapy, with carboplatin substituted for cisplatin.

If second-look assessment was elected at registration, it was performed within 8 weeks after the last cycle of chemotherapy and no later than 29 weeks after study entry. Categories of pathological response were defined as follows: negative (i.e., there was a complete response), positive with microscopic disease only, or positive with grossly visible persistent disease.

STATISTICAL ANALYSIS

The GOG Statistical and Data Center randomly assigned patients to one of the two treatment groups, with stratification according to residual disease (grossly visible disease vs. no visible disease) and the second-look surgery option (selected vs. declined), with use of a permuted block containing three assignments for each regimen. A sample size of 384 eligible patients was set, with sufficient follow-up to observe 208 recurrences (and 208 deaths) before final testing of the primary hypothesis, which was based on the following research question: Does the use of intraperitoneal cisplatin and paclitaxel improve progression-free and overall survival as compared with intravenous cisplatin and paclitaxel? This sample size provided 90 percent statistical power with the use of a one-sided log-rank test,[12] an alpha level of 0.05, and a hazard ratio (for intravenous vs. intraperitoneal administration) of 1.5.[13] Projections indicated that 61 percent of the patients in the intravenous-therapy group would have died by the time of the final analysis.

The primary study end points — progression-free survival and overall survival — were measured from the date of randomization. Survival was measured up to the date of death or, for living patients, the date of last contact. The duration of progression-free survival was the time until progression, death, or the date of last contact, whichever came first. The planned analyses of overall survival and progression-free survival included only eligible patients (on the basis of the intention-to-treat principle). All causes of death were used in the calculation of overall survival. Estimates of the cumulative proportions of survival were based on the Kaplan–Meier procedure.[14] Estimates of the relative risk and confidence intervals for treatment effects with respect to progression and death were generated with use of the Cox model.[15] Primary unadjusted estimates were calculated with use of the two stratification factors as covariates. Adjusted estimates were based on two previously identified additional covariates (age and histologic features).[16]

Eligible women who received at least one cycle of treatment were assessed for toxic effects. Patients in the intraperitoneal-therapy group who had complications related to the intraperitoneal catheter were assessed for toxic effects, regardless

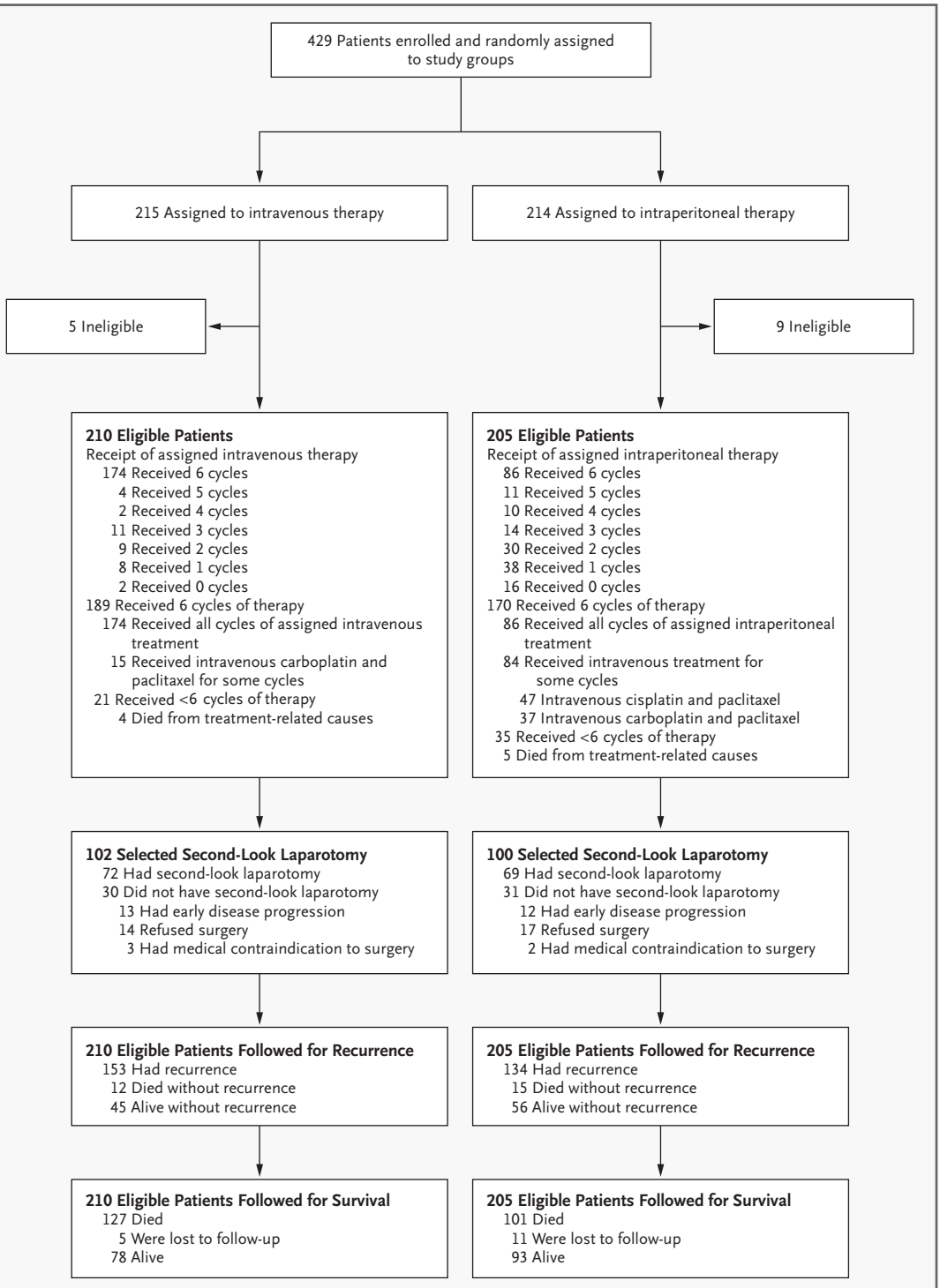

Figure 1. Study Patients.

Table 1. Characteristics of the Patients.*

Characteristic	Intravenous-Therapy Group (N=210)	Intraperitoneal-Therapy Group (N=205)
	no. (%)	
Second-look laparotomy		
Not elected	108 (51)	105 (51)
Elected	102 (49)	100 (49)
Age at diagnosis		
21–30 yr	0	4 (2)
31–40 yr	15 (7)	8 (4)
41–50 yr	43 (20)	52 (25)
51–60 yr	74 (35)	62 (30)
61–70 yr	56 (27)	53 (26)
71–80 yr	19 (9)	24 (12)
>80 yr	3 (1)	2 (1)
Race or ethnic group†		
Hispanic	9 (4)	9 (4)
Asian or Pacific Islander	9 (4)	4 (2)
Black	4 (2)	7 (3)
White	187 (89)	185 (90)
Other	1 (<1)	0
GOG performance status		
0	90 (43)	91 (44)
1	112 (53)	99 (48)
2	8 (4)	15 (7)
Histologic type		
Serous adenocarcinoma	170 (81)	158 (77)
Endometrioid adenocarcinoma	12 (6)	17 (8)
Mixed epithelial carcinoma	11 (5)	14 (7)
Clear-cell carcinoma	9 (4)	11 (5)
Other type	8 (4)	5 (2)
Histologic grade‡		
1	18 (9)	25 (12)
2	83 (40)	72 (35)
3	106 (50)	106 (52)
Gross residual disease		
No	75 (36)	78 (38)
Yes	135 (64)	127 (62)
Disease		
Ovarian cancer	183 (87)	184 (90)
Primary peritoneal cancer	27 (13)	21 (10)

* Because of rounding, not all percentages total 100.
† Race or ethnic group was determined by the investigator or was self-reported at each site.
‡ Five cases were not graded.

of their ability to receive treatment. The Wilcoxon rank-sum test was used to test the independence of the risk of severe and life-threatening toxic effects (grade 0, 1, or 2 vs. grade 3 vs. grade 4) from the assigned treatment.[17]

Quality-of-life assessments from baseline to follow-up (conducted before the fourth cycle, 3 to 6 weeks after the sixth cycle, and 12 months after the sixth cycle) were analyzed with linear models with an unstructured covariance matrix. Patients' age, performance status at randomization, and baseline assessment scores were potential covariates. The restricted maximum likelihood was used to estimate the covariance parameters. Quality of life was a secondary end point. All P values are two-sided.

RESULTS

PATIENTS

Between March 1998 and January 2001, 429 women were randomly assigned to the intravenous-therapy group (215 patients) or the intraperitoneal-therapy group (214 patients) (Fig. 1). Fourteen patients were ineligible (five in the intravenous-therapy group and nine in the intraperitoneal-therapy group) for the following reasons: stage other than optimal stage III (three patients), the presence of a second primary cancer (one patient), a nonepithelial cell type (five patients), a primary cancer other than ovarian or peritoneal carcinoma (one patient), inadequate surgery (two patients), or a tumor with low malignant potential (two patients). Table 1 shows the characteristics of the 415 eligible patients whose data form the basis of this report.

TOXICITY

Of the 210 eligible patients assigned to the intravenous-therapy group, 189 (90 percent) completed six cycles of chemotherapy, and 174 (83 percent) received all six cycles of the assigned intravenous therapy (Fig. 1). Of the 205 eligible patients assigned to the intraperitoneal-therapy group, 170 (83 percent) completed six cycles of chemotherapy, and 86 (42 percent) received all six cycles of the assigned intraperitoneal therapy. For patients in either group who had intolerable toxic effects related to cisplatin, that drug was switched to intravenous carboplatin. The primary reason for discontinuation of intraperitoneal therapy was catheter-related complications.[18] There were

nine treatment-related deaths, four in the intravenous-therapy group and five in the intraperitoneal-therapy group. All nine treatment-related deaths were attributed to infection. Of the five treatment-related deaths in the intraperitoneal-therapy group, three were also partially attributed to the tumor.

Table 2 lists adverse events. Significantly more patients in the intraperitoneal-therapy group than in the intravenous-therapy group had severe or life-threatening (grade 3 or 4) fatigue, pain, or hematologic, gastrointestinal, metabolic, or neurologic toxic effects (P≤0.001).

Table 2. Frequency of Grade 3 or 4 Adverse Events.

Adverse Event	Intravenous-Therapy Group (N=210)	Intraperitoneal-Therapy Group (N=201)*	P Value†
	no. (%)		
Leukopenia‡	134 (64)	152 (76)	<0.001
Platelet count <25,000/mm^3	8 (4)	24 (12)	0.002
Other hematologic event	190 (90)	188 (94)	0.87
Gastrointestinal event	51 (24)	92 (46)	<0.001
Renal or genitourinary event	5 (2)	14 (7)	0.03
Pulmonary event	5 (2)	7 (3)	0.50
Cardiovascular event	10 (5)	19 (9)	0.06
Neurologic event	18 (9)	39 (19)	0.001
Cutaneous change	2 (1)	2 (1)	0.96
Event involving lymphatic system	0	3 (1)	0.07
Fever	8 (4)	19 (9)	0.02
Infection	12 (6)	33 (16)	0.001
Fatigue	9 (4)	36 (18)	<0.001
Metabolic event	15 (7)	55 (27)	<0.001
Pain	3 (1)	23 (11)	<0.001
Hepatic event	1 (<1)	6 (3)	0.05
Other	1 (<1)	6 (3)	0.05

* Four patients did not receive any protocol-based therapy.
† P values were calculated by the Wilcoxon rank-sum test (grades 0, 1, and 2 vs. grades 3 and 4).
‡ A white-cell count below 1000 per cubic millimeter was considered to indicate leukopenia.

PATHOLOGICAL RESPONSES AT SECOND-LOOK LAPAROTOMY

Second-look laparotomy after the completion of therapy was not mandatory, and the results of second-look surgery were not an end point of this study. Of the 415 eligible patients, 202 (49 percent) registered for second-look surgery. The frequency of refusal and the rate of medical contraindication to the procedure were similar in the two groups. The rate of complete pathological response was 41 percent in the intravenous group (35 of 85 patients had such a response) and 57 percent in the intraperitoneal group (46 of 81 patients).

SURVIVAL

The median duration of follow-up was 48.2 months in the intravenous-therapy group and 52.6 months in the intraperitoneal-therapy group, with 5 and 11 patients, respectively, lost-to-follow-up. The median progression-free survival was 18.3 months in the intravenous-therapy group and 23.8 months in the intraperitoneal-therapy group (Fig. 2A and Table 3). The median overall survival was 49.7 and 65.6 months, respectively (Fig. 2B and Table 3). Table 3 lists relative risks, 95 percent confidence intervals, and P values for progression-free and overall survival in the two groups. The adjusted estimates of the relative risk of recurrence and death (0.77 and 0.73, respectively, in the intraperitoneal-therapy group as compared with the intravenous-therapy group) were similar to the primary estimates (0.80 and 0.75, respectively). There was no statistical difference in the risk reduction associated with intraperitoneal therapy between the subgroup with gross visible residual disease and the subgroup with no visible residual disease at initial surgery (Table 3). An analysis that included all randomly assigned patients (eligible and ineligible) yielded negligible changes in the relative-risk estimates.

Before randomization, patients in the intraperitoneal-therapy group reported lower FACT-O (quality-of-life) scores than those in the intravenous group. After adjustments were made for age, performance status, and the baseline FACT-O score, patients receiving intraperitoneal therapy reported worse quality of life before cycle 4 (P<0.001) and three to six weeks after treatment (P=0.009). There were no significant quality-of-life differences between the groups one year after treatment (Table 4). Differences in neurotoxic effects and abdominal discomfort between the two groups have been reported elsewhere.[19,20]

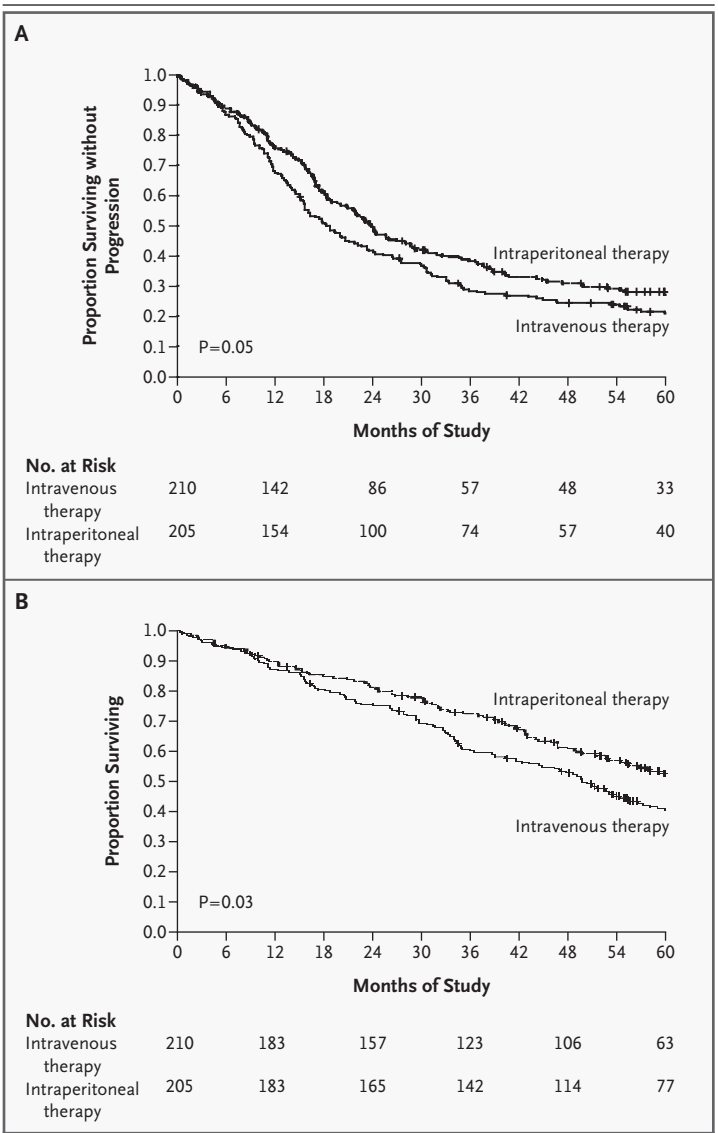

Figure 2. Progression-free and Overall Survival.

Panel A shows progression-free survival and Panel B overall survival among the 415 eligible patients with stage III ovarian cancer who were randomly assigned to treatment with intravenous paclitaxel and cisplatin or to treatment with intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel. Eighty-five percent of the patients either died or were followed for five years. As shown in Panel A, treatment failed in 165 patients in the intravenous-therapy group: 153 (73 percent) had a recurrence, and 12 died without a documented recurrence. Forty-five patients in the intravenous-therapy group had no evidence of disease. Treatment failed in 149 patients in the intraperitoneal-therapy group: 134 (65 percent) had a recurrence, and 15 died without a documented recurrence. Fifty-six patients in the intraperitoneal group had no evidence of disease. As shown in Panel B, in the intravenous-therapy group, 127 patients (60 percent) died and 5 were lost to follow-up. Seventy-eight patients in the intravenous-therapy group were alive. In the intraperitoneal-therapy group, 101 patients (49 percent) died and 11 were lost to follow-up. Ninety-three patients in the intraperitoneal-therapy group were alive.

DISCUSSION

An intensive regimen of intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel significantly improved progression-free survival (P=0.05) and overall survival (P=0.03) among women with newly diagnosed, optimally debulked stage III ovarian cancer. As compared with the intravenous-therapy group, women who received intraperitoneal treatment had a 25 percent reduction in the risk of death. Among all randomized phase 3 trials conducted by the GOG among patients with advanced ovarian cancer, the current trial yielded the longest median survival: 65.6 months, in the group of patients who received intraperitoneal therapy.

Ovarian cancer commonly spreads within the peritoneal cavity; there is a reduced likelihood of substantial hematogenous or lymphatic dissemination. Successful tumor cytoreduction with modern surgical approaches allows chemotherapy to be administered in the setting of low-volume residual disease within the peritoneal cavity. The rationale for intraperitoneal administration is supported by preclinical and pharmacokinetic data and, with this study, a growing body of clinical data. In a previous GOG study, doubling the dose of intravenous cisplatin and cyclophosphamide did not improve survival.[21] Furthermore, the strategy of increasing the dose density or dose intensity of systemic platinum agents is limited by the nonhematologic toxicity of cisplatin and the lack of a reliable platelet growth factor to overcome carboplatin-related thrombocytopenia. These limitations can be overcome, in part, by intraperitoneal administration.

Patients in the intraperitoneal-therapy group had more toxic events than women in the intravenous-therapy group. These toxic events may be attributed to the higher dose of cisplatin in the intraperitoneal-therapy group. The rationale for increasing the cisplatin dose is that capillary uptake of cisplatin from peritoneal surfaces is slow and incomplete, resulting in systemic exposure that is prolonged but lower than that with intravenous administration.[22] The dose of intraperitoneal cisplatin used in this study has previously been given in combination with intravenous paclitaxel[8] and with intravenous cyclophosphamide[7] and in a phase 2 trial of the same regimen[23] with acceptable toxicity. Alternatively, the increased incidence of toxic events

Table 3. Summary of Comparisons between the Treatment Groups.

Variable	Median Duration		No. of Events*		Relative Risk (95% CI)†	P Value
	Intravenous-Therapy Group	Intraperitoneal-Therapy Group	Intravenous-Therapy Group	Intraperitoneal-Therapy Group		
	mo					
Progression-free survival	18.3	23.8	165	149	0.80 (0.64–1.00)	0.05
Gross residual disease	15.4	18.3	115	105	0.81 (0.62–1.05)	0.97‡
No visible residual disease	35.2	37.6	50	44	0.80 (0.54–1.21)	
Overall survival	49.7	65.6	127	101	0.75 (0.58–0.97)	0.03
Gross residual disease	39.1	52.6	95	77	0.77 (0.57–1.04)	0.72‡
No visible residual disease	78.2	NA§	32	24	0.69 (0.41–1.17)	

* Events were a recurrence of disease or death without documented recurrence in the analysis of progression-free survival and death regardless of cause in the analysis of overall survival.
† The relative risk is the risk of recurrence or death in the intraperitoneal-therapy group as compared with that in the intravenous-therapy group. The primary estimate for the entire study group included the covariates of residual-disease status and the second-look surgery option.
‡ The P value was calculated by a test for the homogeneity of relative risk between the two categories of residual-disease status.
§ NA denotes not applicable because the medians for survival had not yet been reached.

in the intraperitoneal-therapy group may be due to the intraperitoneal paclitaxel. Paclitaxel persists in the peritoneum for one week after intraperitoneal administration, suggesting that peritoneal clearance is very slow.[24] Nevertheless, with the dose used in this study, paclitaxel is detectable in the plasma after intraperitoneal administration.[24] It is possible that peritoneal clearance of paclitaxel is altered when the drug is given after intraperitoneal cisplatin, as it was in this study, or that even low blood levels of paclitaxel one week after the administration of intravenous paclitaxel and intra-peritoneal cisplatin can increase toxicity. Careful monitoring of toxicity and the use of contemporary supportive care measures might improve the tolerability of the regimen we used. However, it is not known whether altering the intraperitoneal regimen to decrease toxicity will affect its efficacy.

Given the increased toxicity associated with intraperitoneal therapy, an important secondary outcome of this study was the quality of life. Patients in the intraperitoneal-therapy group reported worse quality of life before cycle 4 and three to six weeks after treatment was completed than did those in the intravenous-therapy group. These differences were not observed one year after treatment was completed, at which time quality-of-life scores had improved relative to baseline in both groups.

A substantial portion of patients in the intraperitoneal-therapy group had toxic effects and treatment intolerance related to the catheter required for intraperitoneal administration. In this group, 48 percent received three or fewer cycles of intraperitoneal treatment, and only 42 percent received all six assigned cycles of intraperitoneal therapy. The type of catheter and the timing of catheter placement were not specified in the study design. A separate, detailed evaluation of intraperitoneal catheter–related outcomes in this study showed that patients who had a left colonic or rectosigmoid resection at the time of initial surgery were less likely to receive all planned doses of intraperitoneal therapy.[18] The single-lumen venous-access catheter attached to an implanted subcutaneous port has been reported to be superior to the fenestrated catheter designed for intraperitoneal use, with minimal fibrous-sheath formation and a markedly reduced risk of small-bowel obstruction or perforation.[25] Thus, standardization of the device to be used and the technique and timing of port implantation could improve the success of intraperitoneal therapy.

Although fewer than half the patients assigned to the intraperitoneal group received six cycles of intraperitoneal treatment, the group as a whole had a significant improvement in survival as compared with the intravenous group. It is possible that most of the benefit of intraperitoneal therapy occurs early, during the initial cycles, or that

Table 4. Mean FACT-O Quality-of-Life Scores in the Two Groups at Each Assessment Point.*

Assessment Point	Intravenous-Therapy Group		Intraperitoneal-Therapy Group		Mean Difference (95% CI)†	P Value
	No. of Patients	Score	No. of Patients	Score		
Before randomization	201	111.9±19.3	198	106.4±20.5	5.0 (1.2 to 8.8)	0.03‡
Before fourth cycle	172	114.7±18.6	148	103.3±19.2	8.9 (5.3 to 12.5)	<0.001§
3–6 Wk after sixth cycle	171	118.4±19.2	159	110.5±21.0	5.2 (1.3 to 9.1)	0.009§
12 Mo after sixth cycle	140	127.2±19.1	139	125.5±19.2	1.2 (–5.1 to 2.8)	0.56§

* Plus–minus values are means ±SD. Lower Functional Assessment of Cancer Therapy — Ovarian (FACT-O) scores (ranging from 0 to 156) indicate poorer quality of life. CI denotes confidence interval.
† The mean difference is the estimated adjusted mean value in the intravenous-therapy group minus the corresponding mean value in the intraperitoneal-therapy group.
‡ The P value was calculated with use of the general linear model, with adjustment for age and performance status at randomization.
§ The P value was calculated with use of the linear mixed model, with adjustment for age, performance status, and baseline FACT-O score.

the benefit of intraperitoneal therapy may be greater if more patients can successfully complete six cycles of treatment. This study was not designed to address the effect of the duration of treatment on clinical outcome, and retrospective analysis of this variable has the potential for bias. Possible means of improving the tolerability of intraperitoneal treatment include identification and exclusion of patients at risk for poor tolerance, modification of the dose of drug used, alteration of the administration schedule, and use of less toxic chemotherapeutic agents. Studies of intraperitoneal carboplatin,[26] of weekly intraperitoneal paclitaxel, and of combinations of intravenous paclitaxel and intraperitoneal docetaxel may identify regimens with improved tolerance. Since modifications that improve tolerability may decrease antitumor efficacy, these approaches will require rigorous testing in randomized trials before they can be recommended.

Including this study, there are now three randomized trials showing that intraperitoneal chemotherapy has a clinical advantage in the treatment of ovarian cancer. Although this advantage comes at the expense of increased toxicity and reduced quality of life during treatment, these results should encourage the use of intraperitoneal chemotherapy in patients with advanced ovarian cancer.

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APPENDIX

The following Gynecologic Oncology Group member institutions participated in this study: the University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, Walter Reed Army Medical Center, Wayne State University, the University of Minnesota Medical School, the University of Mississippi Medical Center, the Colorado Foundation for Medical Care, the University of California Medical Center at Los Angeles, the University of Washington Medical Center, the Hospital of the University of Pennsylvania, the Milton S. Hershey School of Medicine of the Pennsylvania State University, the University of Cincinnati College of Medicine, the University of North Carolina School of Medicine, the University of Iowa Hospitals and Clinics, the University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, the University of California, Irvine, Medical Center, Tufts New England Medical Center, Rush–Presbyterian-St. Luke's Medical Center, the University of Kentucky, National Cancer Institute–Community Clinical Oncology Program, the Cleveland Clinic Foundation, State University of New York at Stony Brook, Washington University School of Medicine, Columbus Cancer Council, the University of Massachusetts Medical Center, the Women's Cancer Center of California, University of Oklahoma, the University of Virginia, the University of Chicago, Tacoma General Hospital, Thomas Jefferson University Hospital, the Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, North Shore University Hospital, Brookview Research, and Ellis Fischel Cancer Center.

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