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ARTICLE

Advanced Ovarian Cancer: Phase III Randomized Study of Sequential Cisplatin–Topotecan and Carboplatin–Paclitaxel vs Carboplatin–Paclitaxel

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Background Topotecan has single-agent activity in recurrent ovarian cancer. It was evaluated in a novel combination compared with standard frontline therapy.

Methods Women aged 75 years or younger with newly diagnosed stage IIB or greater ovarian cancer, Eastern Cooperative Oncology Group Performance Status of 1 or less, were stratified by type of primary surgery and residual disease, treatment center, and age; then randomly assigned to one of the two 21-day intravenous regimens. Patients in arm 1 (n = 409) were administered four cycles of cisplatin 50 mg/m^2 on day 1 and topotecan 0.75 mg/m^2 on days 1–5, then four cycles of paclitaxel 175 mg/m^2 over 3 hours on day 1 followed by carboplatin (area under the curve = 5) on day 1. Patients in arm 2 (n = 410) were given paclitaxel plus carboplatin as in arm 1 for eight cycles. We compared progression-free survival (PFS), overall survival, and cancer antigen-125 normalization rates in the two treatment arms. A stratified log-rank test was used to assess the primary endpoint, PFS. All statistical tests were two-sided.

Results A total of 819 patients were randomly assigned. At baseline, the median age of the patients was 57 years (range = 28–78); 81% had received debulking surgery, and of these, 55% had less than 1 cm residual disease; 66% of patients were stage III and 388 (47.4%) patients had measurable disease. After a median follow-up of 43 months, 650 patients had disease progression or died without documented progression and 406 had died. Patients in arm 1 had more hematological toxicity and hospitalizations than patients in arm 2; PFS was 14.6 months in arm 1 vs 16.2 months in arm 2 (hazard ratio = 1.10, 95% confidence interval = 0.94 to 1.28, $P = .25$). Among patients with elevated baseline cancer antigen-125, fewer in arm 1 than in arm 2 had levels return to normal by 3 months after random assignment (51.6% vs 63.3%, $P = .007$)

Conclusions Topotecan and cisplatin, followed by carboplatin and paclitaxel, were more toxic than carboplatin and paclitaxel alone, but without improved efficacy. Carboplatin plus paclitaxel remains the standard of care for advanced epithelial ovarian cancer.

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Cisplatin plus paclitaxel, and subsequently carboplatin plus paclitaxel, have become the most widely accepted first-line chemotherapy regimens for advanced epithelial ovarian cancer (1–4). Despite the improvements in outcome afforded by this treatment, the great majority of women with ovarian cancer will relapse and eventually die of their disease. One approach to try to improve this treatment is to add a third active agent to the carboplatin–paclitaxel combination. The camptothecin analog, topotecan, has shown activity in the treatment of recurrent ovarian cancer, including platinum-resistant disease (5–9). However, combining topotecan with carboplatin and paclitaxel as a triplet therapy is problematic due to myelosuppression (10). To address this problem, the NCIC Clinical Trials Group (NCIC CTG) tested an approach of sequential doublets of cisplatin plus topotecan followed by carboplatin—paclitaxel as a means of integrating this third agent into the standard regimen. The activity seen in the phase II study of this combination (11) was sufficient to warrant phase III investigation. This report outlines the results of a randomized phase III study that compares standard carboplatin plus paclitaxel to the triple drug combination regimen including topotecan. The trial was conducted by the NCIC CTG, the European Organization for Research and Treatment of Cancer–Gynecologic Cancer Group (EORTC-GCG) and the Grupo de Investigación de Cáncer de Ovario (GEICO) cooperative groups under the

CONTEXT AND CAVEATS

Prior knowledge

Although as a single agent, topotecan has shown some activity against ovarian cancer, it was not known whether adding topotecan to a standard combination treatment for ovarian cancer would improve patient outcomes.

Study design

Here, 819 women with stage IIB or greater ovarian cancer were randomly assigned to carboplatin–paclitaxel or to cisplatin–topotecan followed by carboplatin–paclitaxel. Progression-free survival and overall survival were measured, in addition to adverse effects, quality of life, and CA125 normalization.

Contribution

Patients in the treatment arm that included topotecan had more adverse effects and no improvement in progression-free survival.

Implications

Carboplatin plus paclitaxel remains the best treatment for epithelial ovarian cancer stage IIB or greater.

Limitations

It is too early to determine the effects of the new treatment on overall survival.

From the Editors

auspices of the Gynecologic Cancer Intergroup in women with newly diagnosed advanced epithelial ovarian or fallopian tube or primary peritoneal cancers.

Patients and Methods

Eligibility

Eligible women had newly diagnosed, chemotherapy-naive, epithelial ovarian, fallopian tube, or primary peritoneal cancer and had completed all planned primary surgery. Other entry criteria included: International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IV disease; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; age 18–75 years; adequate hematological reserve (granulocytes $\geq 2 \times 10^9$/L, platelets $\geq 150 \times 10^9$/L) and renal function (creatinine $\leq$ upper normal limit); and written informed consent. Patients were excluded if they had any of the following conditions: borderline ovarian tumors, prior nonsurgical therapy for ovarian cancer, prior history of another malignancy (except nonmelanoma skin cancer, in situ cervical cancer, or a solid tumor treated with curative intent with no evidence of disease for five or more years), clinically apparent myocardial infarction within the proceeding 6 months, second- or third-degree heart block unless a pacemaker had been implanted, contraindication to high volume saline diuresis, preexisting hearing loss, or neuropathy greater than grade 1. The diagnosis of cancer was expected to be based on histological findings; however, cytological diagnosis was also allowed for women who did not have a tissue diagnosis provided that the patient met the following criteria: a pelvic mass with an abdominal metastasis 2 cm in diameter or larger (unless proven stage IV disease), a normal mammogram within the preceding 6 weeks, and a cancer antigen-125 (CA125) to carcinoembryonic antigen ratio of 25 or greater. If the CA125 to carcinoembryonic antigen ratio was less than 25, patients were eligible providing that colonoscopy (or barium enema) and gastroscopy (or barium meal) were negative. Participating institutions had to have obtained required research ethics committee approval to enroll patients on this study. The clinical trial registration number is NCT00028743 (www.clinicaltrials.gov).

Treatment

Patients in arm 1, the experimental arm, were given the following treatment: cisplatin 50 mg/m^2 intravenously over 60 minutes on day 1 followed by topotecan 0.75 mg/m^2 intravenously for 5 days over 30 minutes on days 1 through 5 for four cycles at 3-week intervals. This was then followed by four cycles of intravenous carboplatin (area under the curve = 5) over 30 minutes (or per institutional standard) and paclitaxel 175 mg/m^2 over 3 hours at 3-week intervals. The carboplatin dose was calculated using either the measured glomerular filtration rate by nuclear renogram or a calculated glomerular filtration rate using the Cockcroft formula.

Patients in arm 2, the standard treatment arm, were given carboplatin (area under the curve = 5) as above plus paclitaxel 175 mg/m^2 over 3 hours every 3 weeks for eight cycles. Interval debulking surgery (for those not optimally debulked at the time of study entry) was allowed in both arms after three or four cycles of therapy.

All drugs were administered in solution as per their product monographs with hydration and premedication according to local institutional standards. (The trial protocol did not specify such standards.)

The protocol's dose reduction criteria were the same for both arms. If, in arm 1, granulocytes were less than 0.5×10^9/L for more than 7 days, or platelets less than 25×10^9/L, or there had been febrile neutropenia, or an infection ($\geq$ grade 3) with neutropenia, then topotecan was to be decreased by 25% in the next cycle, with no change in cisplatin dosing. For patients who developed the same findings while on carboplatin plus paclitaxel (cycles 4–8 for arm 1 or cycles 1–8 for arm 2), paclitaxel was to decrease by 25 mg/m^2 and carboplatin was to decrease by 1 area under the curve. Treatment was to be delayed until recovery of blood counts if the granulocytes were less than 1.5×10^9/L or platelets under 100×10^9/L upon the treatment day. Other dose modifications were made based on adverse effects graded using the Common Toxicity Criteria version 2.0 as follows: for grade 3 arthralgia or myalgia, paclitaxel was reduced by 25 mg/m^2, and for grade 4, paclitaxel was stopped; for grade 4 (life threatening) anaphylaxis, the protocol therapy was discontinued; for grade 2 neurotoxicity, paclitaxel was reduced by 25 mg/m^2 and for grade 3 neurotoxicity, the protocol therapy was discontinued; for grade 2 or worse mucositis, paclitaxel was reduced by 25 mg/m^2; for renal toxicity (after rehydration) with creatinine levels at 1–1.5 × upper limit of normal, cisplatin was reduced by 25%, if creatinine levels were greater than 1.5 × upper limit of normal, the protocol therapy was discontinued.

On Treatment Investigations

On day 1 of each cycle, a physical examination was performed and measurements of complete blood count, serum creatinine, aspartate transaminase (or alanine transaminase), and serum CA125

were obtained. On day 15 of each cycle, a complete blood count was performed. More frequent investigations were conducted if they were indicated medically.

Imaging of the abdomen–pelvis (either by computed tomography scan or magnetic resonance imaging) was required postoperatively before cycle 1 treatment to obtain baseline measures, except when no debulking had been undertaken (biopsy ≤ 1 cm or fine needle aspiration only, in which case the preoperative scan was used) or when optimal debulking had been achieved (largest residual lesion <1 cm, in which case no scans were required). Further imaging in all patients, using the same technique throughout, was to be carried out after cycle 4 (or cycle 3 if interval debulking was planned), and then again after cycle 8 or earlier if progression was suspected. Quality of life (QoL) was assessed using the EORTC quality-of-life questionnaires (QLQs) C30 and OV28 module at baseline and then on day 1 at cycles 3, 5 and 7, and at the end of the last cycle.

Post-Treatment Follow-up

All patients were to be observed every 3 months for the first 3 years after the end of treatment, then every 6 months for 2 years, and then annually. History, physical examination, and measurement of CA125 levels were required at each visit. Imaging was not routinely mandated at these time points but instead was performed at the physician's discretion based on CA125 levels and physical examination or symptomatic findings. QoL questionnaires [EORTC QLQ C30 (12) and OV28 module (13)] were to be completed 3 and 6 months after the end of protocol therapy in all patients. The QLQ C30 contains nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. The OV28 module assesses symptoms that may be specific to ovarian cancer or its treatment including abdominal symptoms, peripheral neuropathy, hormonal symptoms, attitude to disease and treatment, and sexual functioning.

Endpoints

The primary endpoint was progression-free survival (PFS), which was defined as the time from random treatment allocation until the time when the first observation of disease progression or death without progression was documented. The Gynecologic Cancer Intergroup definition of progression was used. Both objective progression [using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (14)] and CA125 progression were included (15). Briefly, objective progression was documented on the basis of either a 20% increase in the sum of diameters over the nadir on study or the appearance of new disease. CA125 progression required an increase to at least twice the upper limit of normal (or of the nadir value if normalization was never achieved) confirmed at least 1 week later. If both events occurred in the same patient, the earlier of the two dates was considered the date of progression for the analysis. CA125 values obtained within 4 weeks of surgery or other invasive abdominal procedures (eg, paracentesis) were not to be counted because it is known that these maneuvers could produce rises in CA125.

Secondary endpoints included overall survival (from date of random assignment to death from any cause), toxic effects, QoL assessed by EORTC QLQ C30 (12) and OV28 module (13), objective response rate [in patients with measurable disease as assessed by RECIST criteria), and CA125 normalization rates 3 months after random assignment (16,17)].

Statistical Considerations

Treatment Allocation. Patients were stratified by treatment center, age (≤65 or >65 years), and extent of surgery before treatment allocation (no debulking, no macroscopic residual, macroscopic residual <1 cm, or macroscopic residual ≥1 cm). A computerized minimization procedure, which uses simple randomization only when there are ties between treatment groups, was used to allocate patients randomly 1:1 to one of the two treatments (18).

Sample Size Calculation. Previous trials that investigated platinum–paclitaxel combination therapy in this setting observed a PFS of approximately 16 months. To have an 80% power to detect a 25% improvement in PFS (ie, from a median of 16 months to 20 months; hazard ratio [HR] = 0.8) using a two-sided 5% alpha, one would need to observe, at the time of the final analysis, a total of 631 progression events (defined as above). Random assignment of 800 patients (400 in each group) over 2 years would be expected to lead to the required number of progression events after a further 29 months of follow-up.

Statistical Analysis. PFS and overall survival were compared between the two treatment arms by a stratified log-rank test, and response rates and CA125 normalization rates were compared at 3 months by the Cochran–Mantel–Haenzel test, all adjusting for the three stratification factors (treatment centers within each group combined, age, extent of pre-randomization surgery) at the time of random assignment. All patients randomly assigned were included in the analyses of these endpoints based on intention-to-treat principle. A Cox proportional hazard model, which included, besides treatment and the three stratification factors listed above, stage of disease (II vs III or IV), grade (well or moderate vs poor, undifferentiated or unknown), histology (serous adenocarcinoma vs others), performance status (0 vs 1) as covariates, was used to assess the treatment effect after adjusting for the additional potential predictors and to identify factors predictive of PFS. The assumption of proportionality in Cox model was assessed by Schoenfeld residuals.

All patients who received at least one dose of protocol treatment were included in the safety and treatment exposure analyses. Fisher exact test was used to compare incidence of adverse events between treatment arms. Changes of QoL scores from baseline in each QoL scale at each assessment point were compared between two treatment arms by the Wilcoxon rank sum test. All patients who had both QoL assessment at baseline and the given assessment point were included in the analysis. All comparisons between treatment arms were carried out using two-sided tests at an alpha level of 5%.

Results

Patient Enrollment and Characteristics

This study evaluated a novel topotecan-based triple drug combination regimen compared with standard paclitaxel and carboplatin

in women with advanced ovarian cancer. Between August 31, 2001, and June 29, 2005, a total of 819 patients (471 from the NCIC CTG, 219 from the EORTC-GCG, and 129 from GEICO) were randomly assigned to four cycles of cisplatin and topotecan followed by four cycles of paclitaxel and carboplatin or to eight cycles of paclitaxel and carboplatin. All were included in the intention-to-treat efficacy analysis (Figure 1). After the number of required progression events had been achieved, the database was locked for final analysis on March 5, 2008. At baseline, median age of the patients was 57 years (range = 28–78); 81% had received debulking surgery, and of these 55% had less than 1 cm residual disease; 66% of patients were stage III and 388 (47.4%) patients had measurable disease. The two treatment arms were balanced with respect to prior surgery; residual disease; age; grade; histology; baseline CA125 levels presence of measurable disease; and global QoL, fatigue, and peripheral neuropathy scores (Table 1). There was one patient who was 78-years-old, and primary conclusion remained the same when this patient was excluded from analysis.

Treatment Delivery

Four patients (three in arm 1 and one in arm 2) never received any treatment or withdrew their consent before the first dose of the treatment and were excluded from analyses on treatment exposures and safety. The majority of patients in both treatment arms completed eight cycles of therapy (78% patients in arm 1 and 81% in arm 2). However, 85% of arm 1 patients had at least one cycle delayed as compared with 50% of patients in arm 2. Most delays for arm 1 patients (77%) were in the first four cycles of topotecan–cisplatin and were related to myelosuppression. Dose reductions were similarly more common in arm 1 than in arm 2: 43% vs 18% (Table 2).

Adverse Effects

Common adverse effects seen in the study included gastrointestinal symptoms, myelosuppression, neurological toxicity, and myalgia (Table 3). Patients in arm 1 had substantially more myelotoxicity than patients in arm 2, with an 85% rate of grade 4 granulocytopenia in arm 1 vs 58% in arm 2 with almost all of this differential rate seen during the topotecan portion of the regimen. The rates of febrile neutropenia or infection with grade 3 or 4 neutropenia were 22% among arm 1 patients and 6% among arm 2 patients, and granulocyte colony-stimulating factor use was more common in arm 1 as noted below. Four deaths on study were attributed to sepsis, two in each arm (0.5% of patients). Other toxic effects that were more frequent in arm 1 included thromboembolic events, nausea, and vomiting. Arm 2 patients had substantially more neurosensory effects and allergic reactions. Hospitalization during treatment was more common for arm 1 than arm 2 patients (11.3% cycles vs 7.1% cycles, respectively).

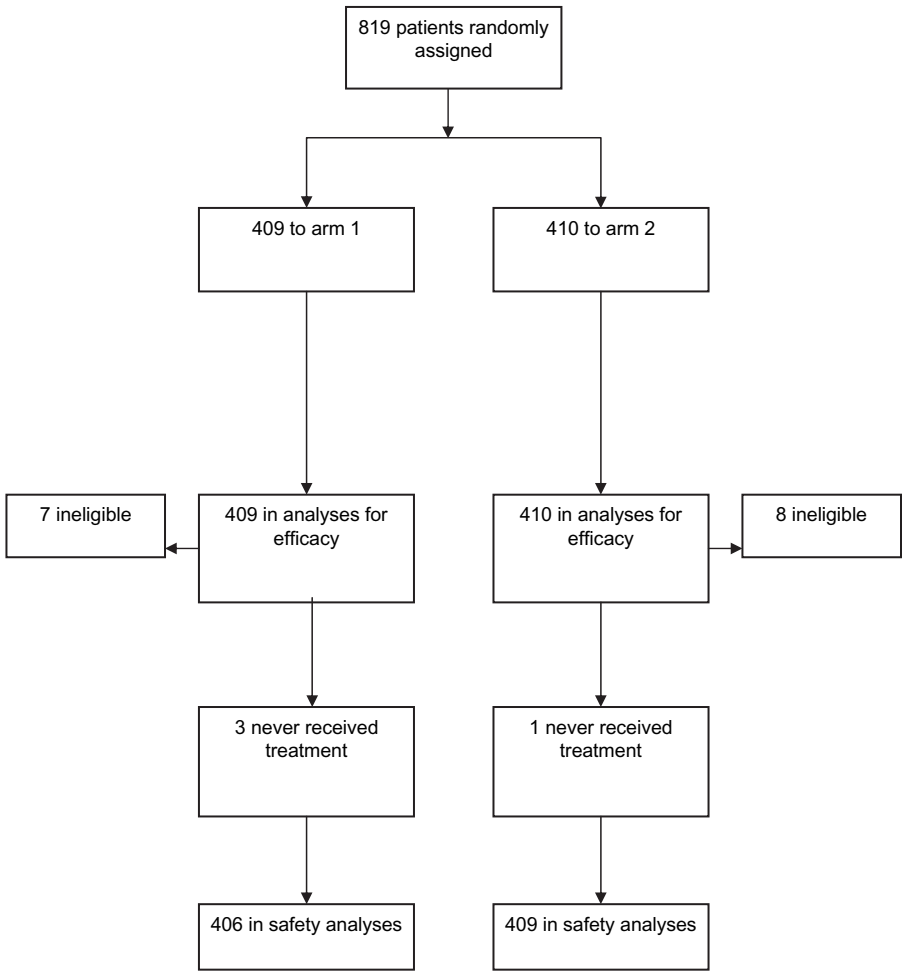

Figure 1. Consolidated Standards of Reporting Trials diagram.

Supportive Care

In keeping with the observations of greater hematological toxicity in arm 1, more patients received hematopoietic growth factors support in that arm. Of the treated patients, 105 (25.8%) on arm 1 received erythropoietin, vs 55 (13.4%) on arm 2. A total of 141 patients (34.7%) in arm 1 received a granulocyte colony-stimulating factor preparation while on therapy vs 56 (13.7%) in arm 2.

Interval Debulking

The study protocol allowed interval debulking to be undertaken in those patients who were not optimally debulked at baseline. A total of 126 patients underwent interval debulking, almost all after cycle 3 or 4. A somewhat greater proportion of arm 2 patients had interval debulking (71 patients; 17.4%) compared with arm 1 patients (55 patients; 13.5%).

Quality of Life

QoL questionnaires were completed at baseline by 90.5% and 87.4% of patients in arms 1 and 2, respectively. At the final 6-month follow-up assessment, compliance rates dropped to 55.9% and 59.4% patients, respectively, with no substantial difference between treatment arms. A full report of QoL analysis will be presented in a separate paper, so only key findings are highlighted here: Over the course of the study, the global QoL score increased both statistically (all $P < .001$) and clinically (defined as a 10-point increase from baseline) from baseline with no statistically significant differences between treatment arms at any assessment time point after baseline (Figure 2,A). Fatigue similarly improved (statistically and clinically as a 10-point decrease from baseline) from baseline with no statistically significant difference between the arms (Figure 2,B). Corroborating the toxicity data, there were statistically significantly more instances of self-reported peripheral neuropathy at cycles 3 and 5 in arm 2 ($P < .001$). By the 6-month follow-up, these scores had substantially decreased from their peaks at the end of treatment in both groups with no between-group differences. However, peripheral neuropathy in both arms remained clinically significantly higher than at baseline (Figure 2,C).

Efficacy

Objective Response. Best response to treatment was assessed in those patients who had measurable disease at baseline: 196 in arm 1 and 193 in arm 2. Overall response rates were statistically significantly lower in arm 1 (133 of 196; 67.9%) than in arm 2 (149 of 193; 77.2%; $P = .04$). Complete responses were seen in 61 (31.1%) arm 1 and 72 (37.3%) arm 2 patients. The difference in overall response rates became borderline significant ($P = .08$) in a logistic regression model that adjusted for both stratification factors and other potential prognostic factors (stage, grade, histology, and performance status).

CA125 Normalization. When the entire randomly assigned population was examined, the proportion of patients with normalized CA125 at or before 3 months after randomization were statistically significantly greater in arm 2 than arm 1 patients (66.3% vs 57.5%; $P = .006$). Restricting this analysis to the 602 patients with elevated

Table 1. Baseline patient characteristics*

Characteristic	Arm 1 (experimental treatment)	Arm 2 (standard treatment)
Total randomly assigned and included in the analysis, No. (%)	409 (100)	410 (100)
Eligible, No. (%)	402 (98.3)	402 (98)
Ineligible, No. (%)	7 (1.7)	8 (2)
Wrong ovarian pathology	2	3
Nonovarian cancer	1	1
Baseline grade III hearing loss	1	2
Relapsed disease	1	0
Wrong stage	1	0
Concurrent serious illness	1	0
Prior malignancy	0	2
Age , median (range), y	57 (28–78)	57 (33–75)
ECOG performance status, No. (%)		
0	138 (34)	125 (31)
1	271 (66)	285 (70)
Cancer site, No. (%)		
Ovary	368 (90)	362 (88)
Fallopian tube	6 (2)	15 (4)
Peritoneal	33 (8)	30 (7)
Other	2	3
Residual disease, No. (%)		
None/micro	90 (22)	92 (22)
Macro < 1 cm	102 (25)	83 (20)
Macro ≥ 1 cm	135 (33)	149 (36)
No debulking	76 (19)	81 (20)
Unknown	6 (1)	5 (1)
FIGO stage, No. (%)		
IIA	1 (0.2)	0 (0.0)
IIB	14 (3.4)	7 (1.7)
IIC	22 (5.4)	26 (6.3)
IIIA	14 (3.4)	12 (2.9)
IIIB	32 (7.8)	43 (10.5)
IIIC	229 (56.0)	210 (51.2)
IV	97 (23.7)	112 (27.3)
Measurable disease, No. (%)	195 (48)	193 (47)
Histology, No. (%)		
Serous	265 (65)	280 (68)
Clear	24 (6)	20 (5)
Mixed	31 (8)	28 (7)
Endometrioid	28 (7)	22 (5)
Mucinous	9 (2)	10 (2)
Unspecified	39 (10)	36 (9)
Other	13 (3)	14 (3)
CA125 at baseline, median (range), U/mL	212 (4–234)	217 (4–424)
Quality of life		
Global		
No. of patients	349	344
Mean score (SD)	53.0 (24.9)	51.9 (23.9)
Fatigue		
No. of patients	353	350
Mean score (SD)	47.6 (26.0)	48.0 (25.2)
Peripheral neuropathy		
No. of patients	347	336
Mean score (SD)	9.7 (14.0)	9.5 (12.7)

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

Table 2. Dose delivery: percentage of planned dose*

	Arm 1				Arm 2	
	Cisplatin	**Topotecan**	**Paclitaxel**	**Carboplatin**	**Paclitaxel**	**Carboplatin**
Total dose planned	200 mg/m^2	15 mg/m^2	700 mg/m^2	AUC 20	1400 mg/m^2	AUC 40
Total dose received, % patients receiving this dose range						
≥90%	79.6	56.9	77.7	79.9	76.0	73.6
≥80, <90	3.2	18.5	9.2	4.9	6.4	8.4
≥60, <80	8.1	14.3	6.0	8.4	8.1	7.4
<60	9.1	10.3	7.1	6.8	9.5	10.6

* AUC = area under the curve.

baseline CA125 values who had at least one follow-up CA125 determination (308 in arm 1 and 294 in arm 2) gave a similar result: normalization rates were 186 of 294 (63.3%) in arm 2 and 159 of 308 (51.6%) in arm 1 ($P = .007$).

The proportion of patients with CA125 normalization at the end of the protocol treatment and at any time during the follow-up were 81.2% and 83.2%, respectively, for arm 2 and 74.3% and 78.2%, respectively, for arm 1. A landmark analysis (excluding those women who had either progression of ovarian cancer before 3 months on study, or who were on study for less than 3 months, or who had no CA125 assessment before 3 months on study) showed that CA125 normalization by 3 months after random assignment was statistically significantly associated with PFS (HR for those with vs without CA125 normalization was 0.29, 95% confidence interval [CI] = 0.25 to 0.34; $P < .001$). CA125 normalization by 6 and 9 months after random assignment was similarly associated with PFS [HR for those with vs without CA125 normalization by 6 months after random assignment = 0.25 (95% CI = 0.20 to 0.31) and HR for those with vs without CA125 normalization by 9 months after random assignment = 0.28 (95% CI = 0.21 to 0.39)].

Progression-free Survival. At the time of analysis (March 5, 2008 database), after a median follow-up of 43 months, 650 progression events had been documented. Kaplan–Meier curves illustrate the PFS outcomes in the study arms (Figure 3). There was no statistically significant difference in the outcomes: the median PFS was 14.6 months and 16.2 months in arms 1 and 2, respectively (HR = 1.10, 95% CI = 0.94 to 1.28; $P = .25$). In a multivariable analysis that adjusted for both stratification factors and other prespecified covariates including stage (II vs III or IV), grade (well or moderate vs poor and undifferentiated or unknown), histology (serous vs others), and ECOG performance status (0 vs 1) as covariates, the treatment difference was still not statistically significant (adjusted HR = 1.11, 95% CI = 0.95 to 1.30, $P = .20$). Debulking, FIGO stage II, and performance status 0 were independent factors that were associated with better survival (Table 4). PFS was statistically significantly different for arm 2 when subdivided by minimal (<1 cm) or bulk residual (≥1 cm) (HR = 1.51, 95% CI = 1.11 to 2.09, $P = .008$). For arm 1, the difference approached statistical significance (HR = 1.21, 95% CI = 0.97 to 1.76, $P = .09$).

Table 3. Adverse effects: worst by patient

	Arm 1	Arm 2	
Adverse events	**Patients, No. (%)**	**Patients, No. (%)**	***P****
Total†	406 (100)	409 (100)	
Nonhematological (all grades)			
Allergic reaction	97 (24)	145 (35)	<.001
Hair loss	358 (88)	368 (90)	.43
Fatigue	355 (87)	339 (83)	.08
Anorexia	177 (44)	164 (40)	.32
Thromboembolic events	28 (7)	8 (2)	<.001
Nausea	341 (84)	314 (77)	.01
Vomiting	233 (57)	167 (41)	<.001
Diarrhea	150 (37)	145 (35)	.66
Stomatitis	166 (41)	153 (37)	.31
Febrile neutropenia or infection with grade 3/4 neutropenia	88 (22)	25 (6)	<.001
Neurosensory	301 (74)	344 (84)	< .001
Myalgia	249 (61)	260 (64)	.51
Abdominal pain	200 (49)	192 (47)	.43
Hematological			
Granulocytes grade 4	344 (85)	234 (58)	<.001
Platelets grade 3 or 4	185 (46)	37 (9)	<.001

* *P* values (two-sided) were calculated using the Fisher exact test.

† Four patients (three in arm 1 and one in arm 2) never received any treatment or withdrew their consent before the first dose of the treatment and were excluded from analyses on treatment exposures and safety.

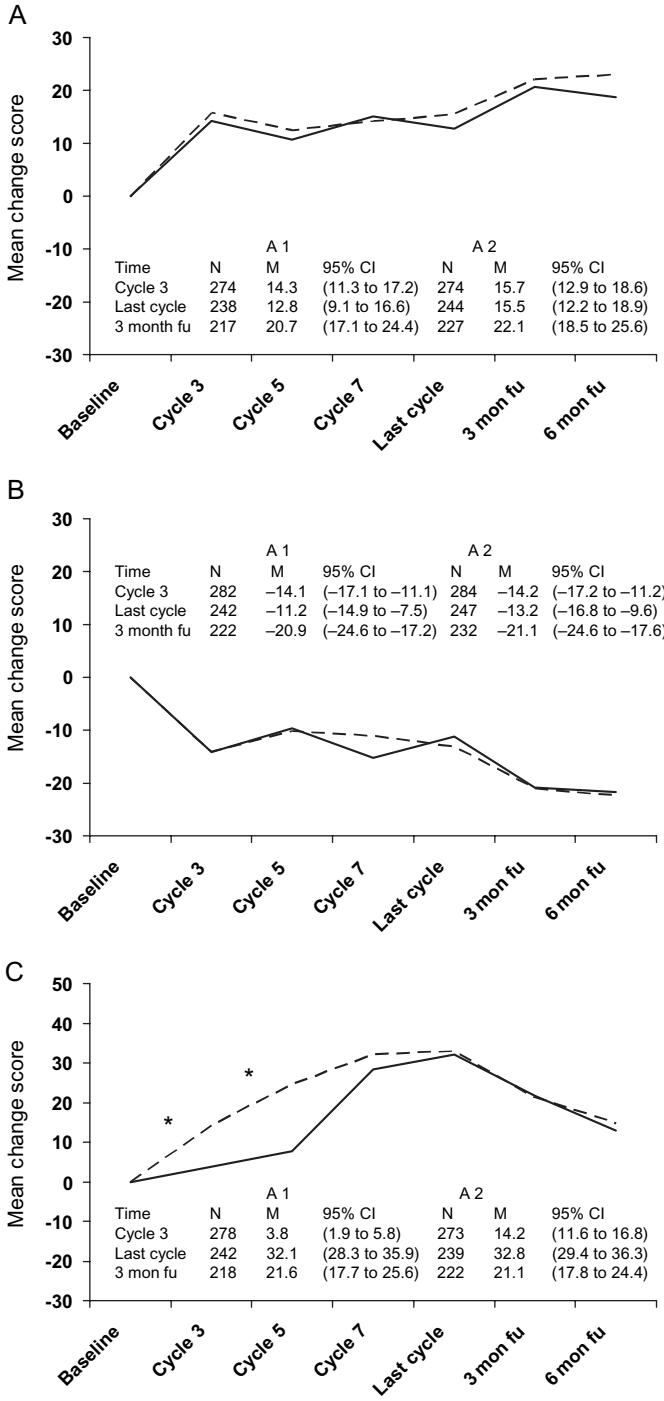

Figure 2. Change in quality-of-life measures from baseline over time by treatment arms. Patients completed questionnaires (European Organization for Research and Treatment of Cancer–quality-of-life questionnaires C30 and OV28 module) at baseline, day 1 on cycles 3, 5, and 7, at the end of the last cycle, and then 3 and 6 months after the end of protocol therapy. The mean change scores from baseline is plotted. In each graph, arm 1 is indicated by a **solid line** and arm 2 is indicated by a **dashed line**. Panels are as follows: **A)** global quality of life, **B)** fatigue, and **C)** peripheral neuropathy. In panel A, positive change indicates improvement, but in panels B and C, negative change indicates improvement. N = number of patients with quality-of-life measurements; M = mean change score, with 95% confidence interval in parentheses; fu = follow-up. The asterisks in panel C indicate a statistical significant difference between the treatment arms ($P < .001$, by a two-sided Wilcoxon rank sum test).

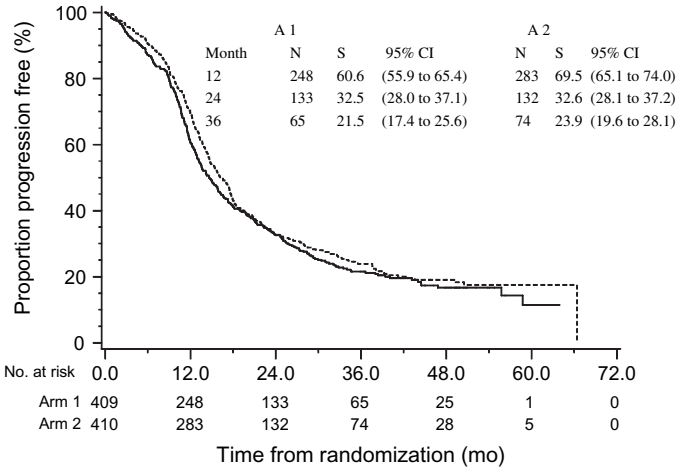

Figure 3. Kaplan–Meier curves for progression-free survival. An event is defined as disease progression or death without progression. In each graph, arm 1 is indicated by a **solid line** and arm 2 is indicated by a **dashed line**. No significant differences were found between the treatment arms. N = number at risk; S = survival percent, with 95% confidence interval in parentheses.

Overall Survival. A total of 406 deaths had been reported at the time of data cutoff with a median overall survival of 42.3 and 42.1 months in arms 1 and 2, respectively (Figure 4). A more definitive analysis of overall survival will be performed when 631 deaths are observed so as to have an 80% power to detect the same hazard ratio for PFS (0.8, which is corresponding to an increase of 8.75 months in median survival from 35 months to 43.75 months) at a two-sided .05 level.

Discussion

In this multinational phase III study for women with advanced (stage IIB or higher) epithelial ovarian, peritoneal, or fallopian tube cancers, first-line therapy with sequential doublets of cisplatin and topotecan followed by carboplatin–paclitaxel was not found to improve PFS compared with standard carboplatin and paclitaxel. Median PFS for patients who received the experimental therapy was 14.6 months vs 16.2 months for those who received the standard therapy ($P = .25$). This outcome parallels that found in Gynecologic Oncology Group (GOG) trial 182, which also evaluated topotecan in sequential doublets as one of four experimental regimens tested (19). Unlike our trial, the GOG study used topotecan in combination with carboplatin, rather than cisplatin. Furthermore, in the GOG study, 3 days of topotecan were given at 1.25 mg/m^2 per day rather than 0.75 mg/m^2 for 5 days, and the drug administration followed the reverse sequence of our study, with the platinum compound given on day 3 rather than on day 1. Although it was our hypothesis that the 5-day schedule of topotecan with day 1 cisplatin administration would be synergistic and show a benefit (20), this did not occur. Because the topotecan-containing arm was associated with increased myelotoxicity, increased rates of neutropenic sepsis and embolic events, increased inconvenience, and did not bring a substantial benefit to QoL, carboplatin–paclitaxel remains the recommended standard of care.

Table 4. Multivariable analysis of progression-free survival*

Factor	N	Adjusted hazard ratio† (95% CI)	*P*
Treatment			
Arm 1	409	1.11 (0.95 to 1.30)	.20
Arm 2	410	1.00	
Groups			
NCIC CTG	471	1.09 (0.92 to 1.28)	.32
Others	348	1.00	
Age			
≤65	619	0.89 (0.74 to 1.06)	.19
>65	200	1.00	
Pre-randomization surgery			
Debulking with no macroscopic residual disease and debulking with macroscopic residual disease (<1 cm)	367	0.49 (0.40 to 0.61)	<.001
Debulking with macroscopic residual disease (≥1 cm)	284	0.83 (0.67 to 1.02)	.07
No debulking	157	1.00	
FIGO stage			
II	70	0.40 (0.27 to 0.59)	<.001
III or IV	749	1.00	
Grade			
Well or moderate	208	0.90 (0.75 to 1.09)	.28
Poor/undifferentiated or unknown	611	1.00	
Histology			
Serous adenocarcinoma	545	0.94 (0.79 to 1.12)	.48
Others	274	1.00	
ECOG performance status			
0	263	0.82 (0.69 to 0.98)	.03
1	556	1.00	

* NCIC CTG = NCIC Clinical Trials Group; FIGO = International Federation of Gynecology and Obstetrics; ECOG = Eastern Cooperative Oncology Group. *P* values (two-sided) were calculated using a stratified log-rank test.

† Hazard ratio relative to last category of each factor.

The cisplatin–topotecan doublet also seemed to be less effective than carboplatin–paclitaxel at least as measured by proportion of patients with CA125 normalization at 3 months, and yet, the early survival outcomes are similar. One explanation could be that the subsequent carboplatin–paclitaxel cycles compensated for this apparent lesser efficacy. However, a comparison of CA125 data later in treatment did not support this explanation. A total of 126 patients in arm 1 (the cisplatin–topotecan containing arm) and 88 on arm 2 had upfront debulking and had continued elevation in CA125 at 3 months after randomization, and only 46 (36.5%) and 35 (39.8%), respectively, had subsequent normalization. Thus, this crude analytic technique did not demonstrate any hint of a compensatory increase.

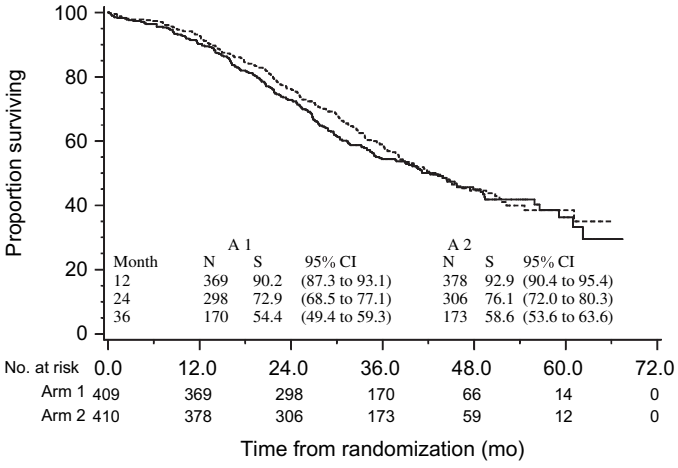

Figure 4. Kaplan–Meier curves for overall survival. An event is defined as death from any cause. In each graph, arm 1 is indicated by a **solid line** and arm 2 is indicated by a **dashed line**. No significant differences were found between the treatment arms. N = number at risk; S = survival percent, with 95% confidence interval in parentheses.

Various other approaches to the integration of topotecan, including administration of triplet combinations and consolidation therapy, have been evaluated in randomized studies (Table 5), but none were associated with an improved outcome compared with standard carboplatin–paclitaxel (19, 21–23). The most sensible explanation for this lack of additional benefit is that the topotecan does not have sufficient cytotoxic impact on cells that are truly resistant to platins or taxanes. Review of the response rates achieved with single-agent topotecan suggests that this is a plausible explanation. For a drug to be truly "noncross resistant," it should have meaningful activity in the refractory setting (ie, when the cancer grows during treatment), and not just in the "resistant" setting (ie, when it recurs shortly after completion of treatment), which includes short duration responders. Four single-agent studies of topotecan included a "refractory" subset, albeit diluted by including patients with stable disease (5–8). Only 9% (15 of 169) of patients responded to topotecan. Thus, although the strategy of adding non–cross-resistant agents remains a reasonable approach to improving outcomes, the actual impact of topotecan in the resistant setting is likely too modest to have an impact. Future cytotoxic drugs need to be able to convincingly kill truly refractory cells before being added to the preexisting standard

Table 5. Other topotecan randomized trials*

Strategy for topotecan integration	Group or country	Stage	No. of patients	PFS, mo		HR	Reference
				Standard	Topotecan		
Sequential	AGO-OVAR/GINECO	IIB–IV	1308	18.5	18.2	0.97	(18)
Consolidation	MITO	1C-IV + response	273	28.4	18.2	1.18	(19)
Triplet	Italy	III > 1 cm/IV	326	16.4	16.8	0.98	(20)
Doublets	GOG	III/IV	1725	16.0	15.4	1.07	(16)
Doublets	Current	IIB–IV	819	16.2	14.6	1.10	—

* AGO-OVAR = Arbeitsgemeinschaft Gynaekologische Onkologie Studeingruppe Ovarialkarzinom; GINECO = Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens; HR = hazard ratio; MITO = Multicenter Italian Trials in Ovarian Cancer; GOG = Gynecologic Oncology Group.

drug or drugs for efficacy testing. The alternate explanation for the failure of the doublet or triplet approaches was that insufficient topotecan was delivered. This argument is refuted by the lack of additional effect seen in the two consolidation studies in which topotecan was delivered at the recommended single-agent dose over 5 days of 1.25 to 1.5 mg/m^2 day.

Phase III studies are time consuming and expensive, both in terms of patients and volunteers and in terms of time and resources. Early discontinuation of trials when the experimental treatment will not offer an improvement in outcomes thus becomes important, and finding an appropriate endpoint upon which to make such judgments has been elusive. Indeed, most often, PFS is the endpoint used for early stopping; yet, with median PFS of approximately 15 months in most frontline ovarian cancer trials, accrual often is completed before sufficient numbers of progression events have been seen to perform an interim analysis. The findings seen in this trial with regard to CA125 normalization rates at 3 months, if confirmed in other randomized studies as being predictive of relative efficacy of treatment arms, suggest that this measure may provide an early opportunity to determine futility of novel regimens in phase III studies. If this relationship between CA125 normalization rates and PFS outcome is confirmed in retrospective analyses of other trials, this measure would potentially be useful to prospectively evaluate not only cytotoxic combination regimens but also regimens that include targeted agents when new regimens are developed that incorporate those types of agents.

Limitations of this study are few: it was adequately powered to detect the postulated difference in the primary endpoint, all patients were included in an intent-to-treat analysis, and sufficient progression events were achieved to assess the primary endpoint. However, the survival data are immature and the final overall results require continued follow-up. Thus, although the conclusions are robust with respect to the lack of benefit of topotecan on PFS, the overall survival effects await later follow-up for this endpoint.

In summary, the use of four cycles of cisplatin–topotecan followed by four cycles of carboplatin–paclitaxel did not provide improved PFS, QoL, or response rates compared with eight cycles of standard carboplatin–paclitaxel in women with newly diagnosed epithelial ovarian cancer at stage IIB and higher. Thus, carboplatin–paclitaxel remains the standard of care for women with newly diagnosed disease.

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