Randomized Phase III Trial of Topotecan Following Carboplatin and Paclitaxel in First-line Treatment of Advanced Ovarian Cancer: A Gynecologic Cancer Intergroup Trial of the AGO-OVAR and GINECO

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For the AGO-OVAR and GINECO

Background: **The combination of carboplatin and paclitaxel is the standard of care for the treatment of ovarian cancer, yet rates of recurrence and death remain high. We performed a prospective randomized phase III study to examine whether sequential administration of topotecan can improve the efficacy of carboplatin and paclitaxel in first-line treatment of advanced epithelial ovarian cancer.** ***Methods:*** **A total of 1308 patients with previously untreated ovarian cancer (International Federation of Gynecology and Obstetrics stages IIB–IV) were randomly assigned to receive six cycles of paclitaxel and carboplatin followed by either four cycles of topotecan (TC-Top; 658 patients) or surveillance (TC; 650 patients) on a 3-week per cycle schedule. The primary endpoint was overall survival, and secondary endpoints were progression-free survival, response rate, toxicity, and quality of life. Time-to-event data were analyzed using the Kaplan–Meier method, and a stratified log-rank test was used to compare distributions between treatment groups. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. Categorical data were compared using a stratified Cochran–Mantel–Haenszel test. All statistical tests were two-sided.** ***Results:*** **Median progression-free survival was 18.2 months in the TC-Top arm versus 18.5 months in the TC arm (stratum-adjusted HR = 0.97 [95% CI = 0.85 to 1.10]; *P* = .688). Median overall survival was 43.1 months for the TC-Top arm versus 44.5 months for the TC arm (stratum-adjusted HR = 1.01 [95% CI = 0.86 to 1.18]; *P* = .885). At 3 years, overall survival in both arms was 57% (58.5% in the TC arm and 55.7% in the TC-Top arm). Compared with patients in the TC arm, patients in the TC-Top arm had more grade 3–4 hematologic toxic effects (requiring more supportive care) and more grade 3–4 infections (5.1% versus 2.7%; *P* = .034) but did not have a statistically significant increase in febrile neutropenia (3.3% versus 3.1%; *P* = .80). Among patients who had measurable disease (TC, n = 147; TC-Top, n = 145), overall (i.e., complete or partial) response was 69.0% (95% CI = 61.4% to 76.5%) in the TC-Top arm and 76.2% (95% CI = 69.3% to 83.1%) in the TC arm (*P* = .166).** ***Conclusions:*** **The sequential addition of topotecan to carboplatin–paclitaxel did not result in superior overall response or progression-free or overall survival. Therefore, this regimen is not recommended as standard of care treatment for ovarian cancer. [J Natl Cancer Inst 2006;98:1036–45]**

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See "Notes" following "References."

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Results of two large phase III trials published in the past decade *(1–3)* showed that cisplatin–paclitaxel is superior to cisplatin–cyclophosphamide in patients with advanced ovarian cancer. Cisplatin–cyclophosphamide has therefore been adopted as the standard first-line treatment for such patients. Subsequently, three prospective randomized trials have shown that carboplatin is at least as effective as, but less toxic than, cisplatin when used in combination with paclitaxel for treating advanced ovarian cancer *(4–6)*. Therefore, the combination of carboplatin and paclitaxel has become the standard of care for patients with advanced ovarian cancer, as was recently confirmed by the 2004 Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference *(7)*.

Despite this progress in treating ovarian cancer over the last several years, most ovarian cancer patients will experience a recurrence and eventually die from their disease *(4–6)*. Thus, better first-line chemotherapy for this disease is needed. One option is to add a third, non–cross-resistant drug to the standard carboplatin and paclitaxel treatment regimen. Several drugs that have been tried include anthracyclins (e.g., epirubicin or pegylated liposomal doxorubicin) and the nucleoside analog gemcitabine *(8–10)*. Recently reported results of two phase III trials investigating carboplatin–paclitaxel with or without epirubicin have shown that the triplet combination had no statistically significant advantage over carboplatin–paclitaxel in terms of response or progression-free or overall survival *(8,9)*. Other clinical trials of treatments for ovarian cancer have completed accrual *(10)*, but their results are not expected soon.

The topoisomerase I inhibitor topotecan is a another reasonable candidate to add to the standard carboplatin and paclitaxel treatment regimen because it displays some non–cross-resistance with paclitaxel *(11)* and it is as effective as either paclitaxel *(12,13)* or pegylated liposomal doxorubicin *(14,15)* in patients with recurrent ovarian cancer. The triplet combination of carboplatin, paclitaxel, and topotecan has been evaluated in two separate single-center phase II studies *(16,17)*. In these studies, carboplatin and paclitaxel were given together at standard doses and schedules and then followed by topotecan, which was well tolerated when given at a dosage of 1.25 mg/m^2/day for 5 days, repeated every 21 days. The use of topotecan following carboplatin–paclitaxel has proven feasible with respect to toxicity, and the data from these two studies *(16,17)* showed that this triplet combination had a low rate of early relapse. Therefore, under the auspices of the Gynecologic Cancer Intergroup (GCIG), the German Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the French Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) performed a prospective randomized phase III study to compare the addition of topotecan to carboplatin–paclitaxel with carboplatin–paclitaxel in first-line treatment of advanced epithelial ovarian cancer. This study was designed to incorporate topotecan as a third drug in a sequential setting in an attempt to avoid the toxicity expected if it were used in a simultaneous triple-drug regimen. Interim results as well as parts of this final analysis were presented at the 2003 and 2005 annual meetings of the American Society of Clinical Oncology *(18,19)*.

Patients and Methods

Patients

This study was designed and performed in accordance with good clinical practice guidelines; German, Austrian, and French drug laws; relevant laws regarding the conduct of clinical studies; and the Declaration of Helsinki. German and Austrian centers of the AGO-OVAR and French centers of the GINECO participated in this study after obtaining approval from their respective local ethics committees. The trial was also certified by the German Cancer Society and was registered in the clinical trials database of the U.S. National Institutes of Health (NCT00102375). All patients provided written informed consent before entry into the study.

Patients with histologically proven epithelial cancer of the ovary or fallopian tube or with extraovarian papillary serous carcinoma {International Federation of Gynecology and Obstetrics [FIGO] stage IIB–IV *(20)*} who had not previously undergone chemotherapy or radiotherapy were eligible for inclusion in this study. All tumors were graded according to the FIGO Grading System *(21)*. Patients had to be enrolled in the study within 6 weeks after undergoing debulking surgery and, at study entry, had to be at least 18 years old and to have adequate hematologic, renal, and hepatic function, defined as follows: absolute neutrophil count of at least 1.5×10^9 cells/L; platelet count of at least 100×10^9 cells/L; serum creatinine level of no more than 1.25 times the upper limit of normal (ULN); bilirubin level of no more than 1.5 times the ULN; and alkaline phosphatase level of no more than three times the ULN. Patients had to have an estimated glomerular filtration rate of at least 60 mL/minute and an Eastern Cooperative Oncology Group performance status *(22)* of 0, 1, or 2. Patients were excluded if they had nonepithelial or mixed epithelial ovarian tumors (e.g., carcinosarcoma) or ovarian tumors with low malignant potential (i.e., borderline tumors); had another malignancy; had previously undergone chemotherapy, immunotherapy, or radiotherapy for ovarian cancer; had severe neuropathy, cardiac arrhythmias, or congestive heart failure; or had received other chemotherapeutic drugs simultaneously or were scheduled to undergo endocrine therapy, simultaneous radiotherapy, or whole-abdominal radiotherapy during the study treatment period.

Patients were randomly assigned to one of the treatment arms and then stratified according to residual tumor size and FIGO stage. Stratum 1 included patients who had FIGO stage IIB–III disease and a residual tumor size of less than or equal to 1 cm. Stratum 2 included patients who had FIGO stage IIB–III disease with a residual tumor size of more than 1 cm or who had FIGO stage IV disease.

Regular monitoring of the participating centers was performed by trained field monitors who checked all data collected on case report forms against each patient's medical records as well as against reviews of the surgeon's and pathologist's reports (i.e., 100% monitoring). Quality-assurance measures consisted of extensive plausibility checks.

Treatment Regimens

Patients were randomly assigned to receive paclitaxel and carboplatin (TC arm) or paclitaxel and carboplatin followed by topotecan (TC-Top arm). In both arms, patients received six cycles of paclitaxel (175 mg/m^2 per cycle, administered intravenously over 3 hours) and carboplatin (area under the curve [AUC] of 5 mg • mL^{-1} • min^{-1} per cycle, administered intravenously over 30–60 minutes). Chemotherapy cycles had a length of 21 days. All patients could receive up to four additional cycles of carboplatin–paclitaxel if recommended by the physician. However, for patients in the TC-Top arm, these additional cycles

had to be given before topotecan was administered. Patients in the TC-Top arm received four cycles of topotecan (1.25 mg/m^2 administered intravenously over 30 minutes on each of days 1–5 of the cycle) after they had completed all their carboplatin–paclitaxel cycles. Again, the length of the cycles was 21 days. The carboplatin dose was calculated according to the method of Calvert et al. *(23)*, and the glomerular filtration rate was estimated according to the formula described by Jelliffe *(24)*. The maximal absolute dose given to each patient was limited to 385 mg for paclitaxel, 800 mg for carboplatin, and 2.7 mg/day for topotecan.

Dose reductions were allowed depending on predefined levels of hematologic or nonhematologic toxic effects as follows: levels 1 and 2 toxic effects, carboplatin reduced to AUC = 4 mg • mL^{-1} • min^{-1} for level 1 or 2 toxicity; paclitaxel reduced to 150 mg/m^2 (for level 1 toxicity) or to 135 mg/m^2 (for level 2 toxicity); and topotecan reduced to 1 mg/m^2 (for level 1 toxicity) or to 0.75 mg/m^2 (for level 2 toxicity). Treatment cycles were delayed if the patient's absolute neutrophil count was less than 1.5×10^9 cells/L or the platelet count was less than 100×10^9 cells/L. Primary prophylaxis with the use of granulocyte colony-stimulating factor (G-CSF) was not recommended; however, supportive G-CSF treatment could be initiated at the discretion of the patient's physician if the patient's absolute neutrophil count recovery took longer than 36 days.

All patients received premedication in the form of one dose of dexamethasone (20 mg), clemastine (2 mg), and ranitidine (50 mg), which was administered intravenously immediately before the paclitaxel infusion; patients in the TC-Top arm also received one dose of dexamethasone (20 mg), which was administered intravenously immediately before the topotecan infusion. Antiemetic prophylaxis for both study arms consisted of serotonin type 3 receptor antagonists and corticoids. In case of disease progression during therapy, patients went off protocol treatment.

Toxicity and Quality-of-Life Measures

Grading of adverse events and toxic effects was based on the National Cancer Institute (NCI) Common Toxicity Criteria (CTC; version 2.0) *(25,26)*. All observed toxic effects were recorded continuously; blood chemistry parameters were measured before each treatment cycle and hematologic parameters were measured weekly. Quality of life was measured according to the global health status/quality-of-life score of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires QLQ-C30 (version 3.0) and QLQ-OV28 [version 1.0; *(27–29)*]. Patients used these questionnaires to assess their health-related quality of life before the start of treatment, after every other treatment cycle, after the last treatment cycle, and at 3 and 6 months after the end of treatment. The answers were scored according to EORTC guidelines *(30)*. Imaging methods (i.e., ultrasound, x-ray, computed tomography, or magnetic resonance imaging) were used to measure tumors at the following time points: before patients went on study (baseline); during the study (if appropriate); in patients who had measurable or evaluable disease after cycle 6 of carboplatin–paclitaxel and in patients in the TC-Top arm after cycle 4 of topotecan; and/or at the end of treatment. The same tumor assessment method that was used for the baseline measurement was used for each subsequent evaluation. Tumor response was graded according to the definitions of the World Health Organization *(31)*. Second-look surgery was allowed but was explicitly not recommended. Patients were followed up every 3 months during the first 2 years after the end of treatment and every 6 months until the fifth year. Thereafter, follow-up visits were performed yearly until death or loss to follow-up.

Randomization

Within each stratum, randomization lists for each study center were prepared before the start of the trial by using permuted blocks of randomly varying size. Randomization was carried out by the offices of AGO-OVAR in Germany and GINECO in France on the basis of patient data that the participating study centers provided.

Statistical Analyses

The primary endpoint of this trial was overall survival. Secondary endpoints were progression-free survival, response rate, toxicity, and quality of life. The trial was designed to detect an 8% absolute increase in 3-year survival in the TC-Top group (i.e., survival improvement from 50% in the TC group to 58% in the TC-Top group) with 80% power at a 5% statistical significance level (two-sided) using a stratified log-rank test, which required at least 541 events. Overall survival was defined as the time from randomization to death from any cause; survivors were censored on the date they were last known to be alive. Progression-free survival was defined as the time from randomization to disease progression or death from any cause; patients who were still alive without progressive disease at the time of analysis were censored on the date of their last follow-up. Overall tumor response rate was defined as the number of patients who had a partial or complete response [as defined by the World Health Organization *(31)*] divided by the number of patients for whom the response could be assessed. Toxicity was measured by examining the frequency of grade 1–4 toxic effects, graded according to the NCI-CTC and evaluated using the worst CTC score over all courses within patients. Time-to-event data were analyzed using the Kaplan–Meier method, and the stratified log-rank test was used to compare distributions between treatment groups. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. The proportional hazards assumption was checked visually from the survival plots and log–log plots of survival. We also included an interaction term of therapy and time in the Cox model to test for violations of the proportional hazards assumption, but the interaction was not statistically significant. We therefore concluded that the data conformed to the proportional hazards assumption. The stratified Cochran–Mantel–Haenszel test was used to compare categorical data. All P values are two-sided. Efficacy analyses were performed on all randomly assigned patients (i.e., on an intention-to-treat basis). Patients who received at least one treatment cycle were included in the safety analysis. Patients who completed at least one QLQ-C30 questionnaire were included in the quality-of-life analysis. All statistical analyses were performed using SAS statistical software (version 8.2; SAS Institute, Cary, NC).

Results

Patients

Between December 1999 and March 2002, 1388 patients were screened for study eligibility by the AGO-OVAR and GINECO study offices. Of the 1308 patients who were enrolled in the study, 762 patients fulfilled the criteria for stratum 1 and 546

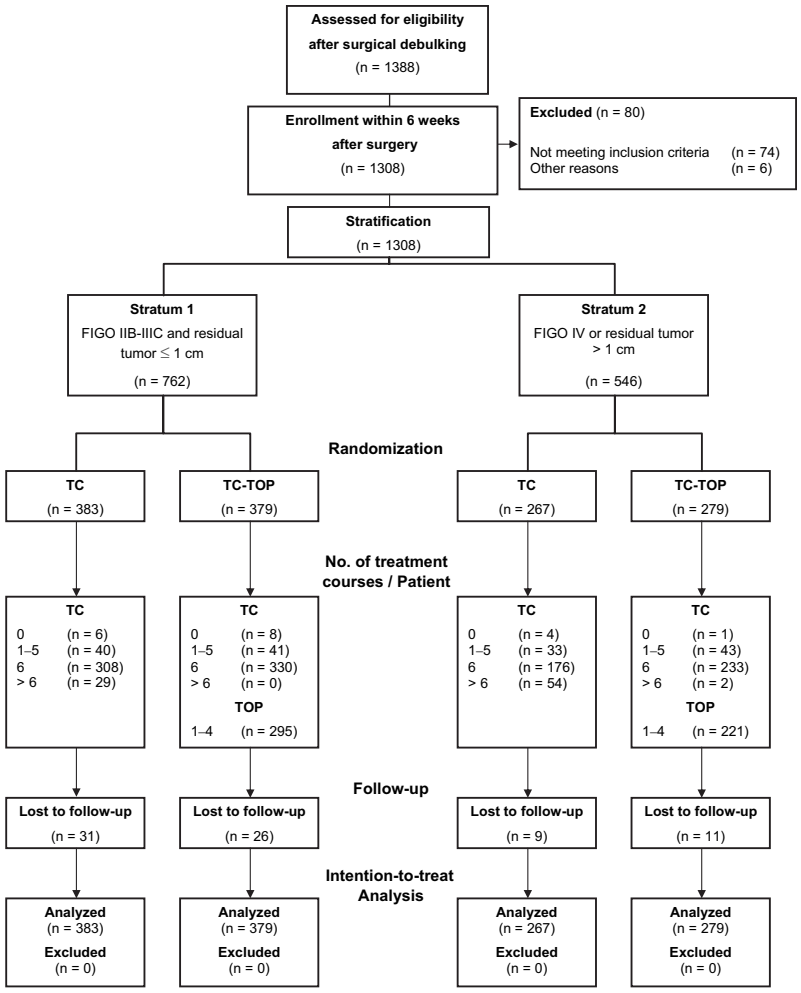

Fig. 1. CONSORT diagram of the trial profile. FIGO = International Federation of Gynecology and Obstetrics; TC = carboplatin–paclitaxel; TC-TOP = carboplatin–paclitaxel–topotecan; TOP = topotecan.

patients fulfilled the criteria for stratum 2 (Fig. 1). After giving written informed consent, 650 patients were randomly assigned to the TC arm and 658 patients were randomly assigned to the TC-Top arm. Data were available for 1287 patients (639 patients in the TC arm and 648 patients in the TC-Top arm) for the analysis of toxicity. A total of 292 patients (147 patients in the TC, 145 patients in the TC-Top arm) qualified for the evaluation of response to treatment. The treatment arms were well balanced with respect to baseline patient characteristics (Table 1).

Treatment Compliance

A total of 9453 treatment cycles were administered, 3889 in the TC arm and 5564 in the TC-Top arm. A total of 1289 (99%) patients received at least one cycle of treatment. In both arms, nearly 90% of patients (87% of those in the TC arm and 86% of those in TC-Top arm) received at least six cycles of carboplatin–paclitaxel. Of the 516 patients who received at least one cycle of topotecan, 458 (89%) received four cycles, corresponding to 70% of all patients in the TC-Top arm.

Treatment delays of 7 days or longer occurred more often in the TC-Top arm (14.4% of cycles 1–10 delayed) than in the TC arm (8.2% of cycles 1–6 delayed) ($P<.001$); the treatment delays in the TC-Top arm were due mainly to delays in topotecan treatment (25.9% of topotecan cycles, cycles 7–10, delayed). Similarly, the frequency of dose reductions was higher in the TC-Top arm during treatment with topotecan (5.8% of topotecan courses, cycles 7–10, compared with 1.9% of TC cycles in the TC arm, cycles 1–6, and 3.5% in the TC-Top cycles 1–10 [$P<.001$]). The mean doses of paclitaxel for the TC arm and the TC-Top arm were 170.4 mg/m^2 and 171.4 mg/m^2, respectively; the mean carboplatin dose was AUC of 5 mg • mL^{-1} • min^{-1} per cycle in both arms. The mean daily dose of topotecan was 1.2 mg/m^2. These amounts correspond to mean dose intensities of 94.3% and 94.1% for paclitaxel and 94.9% and 95.0% for carboplatin in the TC arm and TC-Top arm, respectively. The mean dose intensity for topotecan was 90.0%.

Treatment-Induced Toxicity

There were no major differences between the study arms with respect to the proportion of patients with hematologic (Table 2) or nonhematologic toxic effects over the first six courses of treatment (Table 3). However, when we compared the two arms over the entire course of treatment (i.e., cycles 1–6 in the TC arm and cycles 1–10 in TC-Top arm), grade 3 or 4 hematologic toxic effects, including anemia, leukocytopenia, neutropenia, and thrombocytopenia, were statistically significantly more frequent in the TC-Top arm than in the TC arm. Consequently, more patients treated with TC-Top than with TC received blood transfusions, antibiotics, and/or G-CSF. Over the entire course of treatment (i.e., cycles 1–6 in the TC arm and cycles 1–10 in TC-Top arm), there were more grade 3 or 4 infections in the TC-Top arm than in the TC arm (5.1% versus 2.7%; $P = .034$), but the frequency of

Table 1. Baseline patient characteristics*

Characteristic	TC arm	TC-TOP arm	Total
No. of patients (%)	650 (49.7)	658 (50.3)	1308 (100)
Median age, y (range)	60 (20–81)	60 (20–81)	60 (20–81)
FIGO stage, n (%)			
Unknown	1	1	2
IB	1 (0.2)	0 (0.0)	1 (0.1)
IIA	0 (0.0)	1 (0.2)	1 (0.1)
IIB	24 (3.7)	25 (3.8)	49 (3.8)
IIC	30 (4.6)	34 (5.2)	64 (4.9)
IIIA	30 (4.6)	21 (3.2)	51 (3.9)
IIIB	69 (10.6)	79 (12.0)	148 (11.3)
IIIC	395 (60.9)	376 (57.2)	771 (59.0)
IV	100 (15.4)	121 (18.4)	221 (16.9)
Postoperative residual tumor size, n (%)			
Unknown	61	61	122
≤1 cm	394 (66.9)	405 (67.8)	799 (67.4)
>1 cm	195 (33.1)	192 (32.2)	387 (32.6)
Stratum†, n (%)			
1	383 (58.9)	379 (57.6)	762 (58.3)
2	267 (41.1)	279 (42.4)	546 (41.7)
Histology, n (%)			
Unknown	1	1	2
Serous/papillary	457 (70.4)	465 (70.8)	922 (70.6)
Endometrioid	54 (8.3)	57 (8.7)	111 (8.5)
Mucinous	28 (4.3)	24 (3.7)	52 (4.0)
Other	110 (17.0)	111 (16.9)	221 (16.9)
Histologic grade‡, n (%)			
Unknown	70	67	137
1	46 (7.9)	42 (7.1)	88 (7.5)
2	203 (35.0)	202 (34.2)	405 (34.6)
3	331 (57.1)	347 (58.7)	678 (57.9)
ECOG performance status, n (%)			
Unknown	1	8	9
0	240 (37.0)	227 (34.9)	467 (36.0)
1	346 (53.3)	354 (54.5)	700 (53.9)
2	63 (9.7)	67 (10.3)	130 (10.0)
3	0 (0.0)	1 (0.2)	1 (0.1)
4	0 (0.0)	1 (0.2)	1 (0.1)

*TC = paclitaxel/carboplatin treatment; TC-TOP = paclitaxel/carboplatin/topotecan treatment; FIGO = International Federation of Gynecology and Obstetrics; ECOG = Eastern Cooperative Oncology Group.

†Stratum 1 = FIGO stages IIB–IIIC and residual tumor size less than or equal to 1 cm; Stratum 2 = FIGO stage IV or residual tumor size of greater than 1 cm.

‡FIGO Grading System *(21)*.

febrile neutropenia did not differ between treatment arms (3.1% for TC versus 3.3% for TC-Top; $P = .80$).

Quality-of-Life Measures

We analyzed quality of life only with respect to the global health score because the use of topotecan following carboplatin–paclitaxel induced statistically significantly more toxicity without adding benefit regarding efficacy. Among patients who qualified for the quality-of-life analysis, there was no statistically significant difference in global health scores between the 573 patients who received TC and the 581 patients who received TC-Top, either during treatment or during follow up (data not shown).

Response to Treatment and Survival

The 359 patients (27.5%) who had measurable disease at study entry qualified for evaluation of response to treatment. Of those, response to treatment could be assessed in 292 patients (22.3%). A total of 112 (76.2%) of the 147 assessable patients in the TC arm had a complete or partial response, compared with 100 (69%) of the 145 assessable patients in the TC-Top arm (Table 4). There was no statistically significant difference between treatment arms in the proportion of patients who had a complete or partial response ($P = .166$).

The median follow-up time for surviving patients in both groups was 42 months (range = 0–61 months). A total of 77 patients (5.9%) were lost to follow-up, 44 of them before disease progression.

A total of 947 patients (72.4%) experienced disease progression or recurrence during treatment or follow-up. Median progression-free survival time was 18.5 months (95% CI = 16.8 to 19.9 months) in the TC arm and 18.2 months (95% CI = 16.6 to 20.7 months) in the TC-Top arm (Fig. 2, A). The stratum-adjusted hazard ratio was 0.97 (95% CI = 0.85 to 1.10; stratified log-rank $P = .688$). Among the patients in stratum 1, median progression-free survival time was 28.6 months (95% CI = 24 to 33.2 months) in the TC arm and 26.4 months (95% CI = 22.5 to 30.1 months) in the TC-Top arm, corresponding to a hazard ratio of 1.02 (95% CI = 0.85 to 1.22; $P = .844$). Among the patients in stratum 2,

Table 2. Hematologic toxic effects and associated supportive care*

	Treatment group, cycle range								
	TC, cycles 1–6		TC-TOP, cycles 1–6		TC-TOP, cycles 7–10		TC-TOP, cycles 1–10		
Effect	n	%	n	%	n	%	n	%	P†
Toxicity									
Anemia	40	6.6	50	8.1	77	15.4	109	17.6	<.001
Thrombopenia	33	5.4	51	8.3	142	28.5	167	26.9	<.001
Leukopenia	173	28.2	188	30.5	260	52.0	335	53.8	<.001
Neutropenia	295	54.8	319	59.4	324	78.1	416	75.5	<.001
Supportive care									
Antibiotics	84	13.1	75	11.6	57	11.0	121	18.7	.0057
G-CSF	87	13.6	83	12.9	164	31.7	196	30.3	<.001
Transfusion pRBCs	105	16.4	124	19.2	195	37.7	245	37.9	<.001

*Data reflect the number of patients who had at least one occurrence of the indicated grade 3 or 4 toxicity according to the National Cancer Institute Common Toxicity Criteria [version 2 *(25,26)*]. If patients received pRBCs, antibiotics, or G-CSF, this was coded as a toxicity of grade 3; if not, it was coded as grade 0. TC = paclitaxel–carboplatin treatment; TC-TOP = paclitaxel–carboplatin–topotecan treatment; pRBCs = packed red blood cells; G-CSF = granulocyte colony-stimulating factor.

†Two-sided *P* value for differences in the proportions of patients with grades 3 or 4 toxicity between TC cycles 1–6 and TC-TOP cycles 1–10 (stratified Cochran–Mantel–Haenszel test).

Table 3. Nonhematologic toxic effects by treatment arm and cycle range*

	Treatment arm, cycle range								
	TC, cycles 1–6		TC-TOP, cycles 1–6		TC-TOP, cycles 7–10		TC-TOP, cycles 1–10		
Toxicity	n	%	n	%	n	%	n	%	P†
Auditory/hearing	4	0.8	3	0.6	4	1.0	4	0.8	.94
Allergic reaction/ hypersensitivity	12	1.9	25	3.9	0	0.0	25	3.9	.04
Cardiovascular									
Arrhythmia	4	0.7	12	1.9	6	1.2	13	2.1	.03
General	4	0.7	2	0.3	0	0.0	2	0.3	.39
Edema	2	0.3	6	0.9	0	0.0	6	0.9	.17
Alopecia‡	575	93.0	593	93.8	452	90.4	595	94.2	.40
Constipation	52	8.4	60	9.5	29	5.8	75	11.8	.043
Diarrhea	17	2.8	15	2.4	4	0.8	17	2.7	.93
Nausea	23	3.7	21	3.3	7	1.4	27	4.3	.63
Stomatitis/mucositis	2	0.3	4	0.6	2	0.4	6	1.0	.16
Emesis/vomiting	14	2.3	13	2.1	5	1.0	18	2.8	.54
Infections	17	2.7	16	2.5	16	3.2	32	5.1	.03
Febrile neutropenia	19	3.1	5	0.8	16	3.2	21	3.3	.80
Neuropathy									
Cranial	6	1.2	4	0.8	3	0.7	7	1.4	.84
Sensory	32	5.2	28	4.4	12	2.4	35	5.5	.78
Pain									
Myalgia	22	3.6	15	2.4	3	0.6	18	2.8	.49
Other	43	7.0	49	7.8	14	2.8	59	9.3	.12
Dyspnea	25	4.0	25	3.9	18	3.6	38	6.0	.11
Renal§	6	1.0	2	0.3	1	0.2	3	0.5	.28

*Data reflect the number of patients who had at least one occurrence of the indicated grade 3 or 4 toxicity according to the National Cancer Institute Common Toxicity Criteria [version 2 *(25,26)*]. TC = paclitaxel–carboplatin treatment; TC-TOP = paclitaxel–carboplatin–topotecan treatment.

†Two-sided *P* value for differences in the proportions of patients with grades 3 or 4 toxicity between TC cycles 1–6 and TC-TOP cycles 1–10 (stratified Cochran–Mantel–Haenszel test).

‡The proportion of patients with grade 2 alopecia is reported.

§As determined by increased serum creatinine levels.

median progression-free survival time was 13.1 months in both arms (95% CI = 11.7 to 14.6 months for the TC arm and 12 to 14.8 months for the TC-Top arm), corresponding to a hazard ratio of 0.93 (95% CI = 0.78 to 1.12; *P* = .446).

A total of 625 patients (47.8%) died while undergoing treatment or during follow-up (Fig. 2, B). Median overall survival time was 44.5 months (95% CI = 39.0 to 51.5 months) in the TC arm and 43.1 months (95% CI = 37.6 to 48.7 months) in the TC-Top arm. The stratum-adjusted hazard ratio was 1.01 (95% CI = 0.86 to 1.18; stratified log-rank *P* = .885). The estimated 3-year survival rates were 57.1% (95% CI = 54.3% to 59.9%) for both arms, 58.5% (95% CI = 54.4% to 62.3%) for the TC arm, and 55.7% (95% CI = 51.6% to 59.5%) for the TC-Top arm. The overall survival curves by treatment group within strata 1 and 2 are shown in Figs. 3, A and 3, B, respectively. In stratum 1, median overall survival time was 56.5 months (95% CI = 54.1 months to ∞) for the TC arm, whereas in the TC-Top arm, the median survival time had not yet been reached at the time of this analysis. However, the lower limit of the 95% confidence interval was 52.6 months. The corresponding hazard ratio was 1.08 (95% CI = 0.85 to 1.38; *P* = .512). The estimated 3-year survival rates were 70.7% (95% CI = 65.6% to 75.2%) for the TC arm and 66.3% (95% CI = 61.1% to 71.1%) for the TC-Top arm. In stratum 2, median overall survival time was 28.6 months (95% CI = 24.7 to 32.6 months) for the TC arm and 27.2 months (95% CI = 23.9 to 33.7 months) for the TC-Top arm, corresponding to a hazard ratio of 0.96 (95% CI = 0.78 to 1.18; *P* = .706). The estimated 3-year survival rates were 41.3% (95% CI = 35.2% to

Table 4. Clinical tumor response to treatment*

	TC arm		TC-TOP arm		Total	
Response	n	%	n	%	n	%
Unknown	33		34		67	
Complete	62	42.2	56	38.6	118	40.4
Partial	50	34.0	44	30.3	94	32.2
Stable disease	18	12.2	25	17.2	43	14.7
Progressive disease	17	11.6	20	13.8	37	12.7
Overall response†	76.2%		69.0%		72.6%	
(95% CI)	(69.3% to 83.1%)		(61.4% to 76.5%)		(67.5% to 77.7%)	

*TC = paclitaxel–carboplatin treatment; TC-TOP = paclitaxel–carboplatin–topotecan treatment; n = number; CI = confidence interval.

†Two-sided *P* values for differences in the proportions of patients with overall response (complete or partial response) between treatment arms: *P* = .1663 (chi-square test), *P* = .1901 (Fisher's exact test), and *P* = .1487 (stratified Cochran–Mantel–Haenszel test).

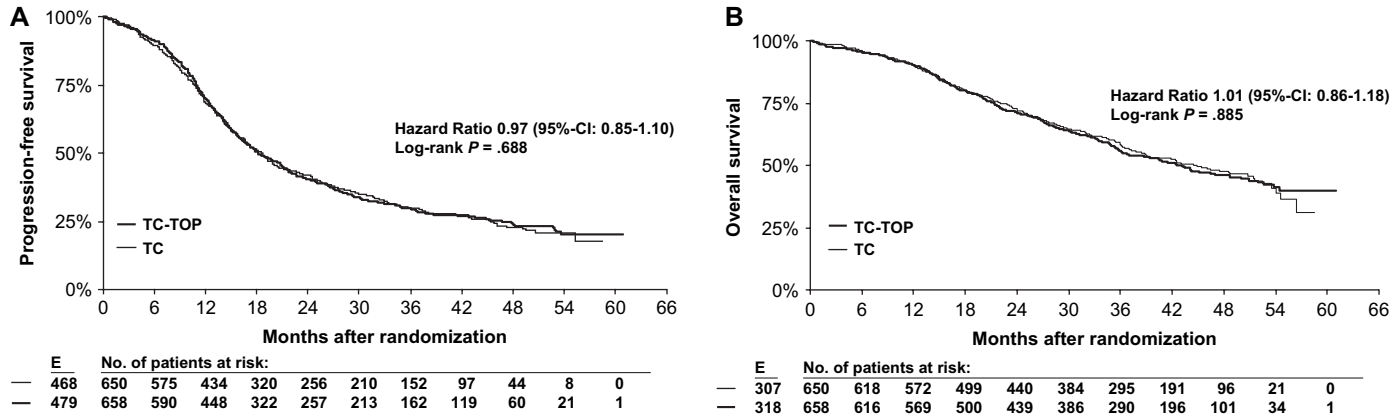

Fig. 2. Kaplan–Meier survival curves for all randomly assigned patients by treatment group. (**A**) Progression-free survival. (**B**) Overall survival. TC = carboplatin–paclitaxel; TC-TOP = carboplatin–paclitaxel–topotecan; TOP = topotecan; E = number of events; CI = confidence interval.

47.3%) for the TC arm and 41.1% (95% CI = 35.1% to 47.0%) for the TC-Top arm.

Because only 70% of the patients who were randomly assigned to the TC-Top arm completed four cycles of topotecan, we performed a per-protocol analysis of survival among patients who completed at least six cycles of carboplatin–paclitaxel and had no progression of disease within 3 weeks after the sixth cycle of carboplatin–paclitaxel (555 patients in the TC arm and 558 patients in the TC-Top arm). Also, patients in the TC-Top arm had to have received at least one cycle of topotecan (507 patients in the TC-Top arm). The stratum-adjusted hazard ratio was 1.01 (95% CI = 0.84 to 1.21; stratified log-rank $P = .884$), which is in line with the results of the intention-to-treat analysis.

Treatment for recurrence was similar in the two study arms: Approximately 29% of patients with recurrences in each arm were treated with pegylated liposomal doxorubicin, 25% with platinum-based combination therapy, 14% with platinum monotherapy, 10% with alkylating agents, and 7% with gemcitabine. Only 9% were treated with topotecan (14% in the TC arm versus 4% in the TC–Top arm).

Discussion

Despite the implementation of carboplatin and paclitaxel as the standard of care in first-line treatment of ovarian cancer, rates of recurrence and death remain high. Thus, better treatments for this disease are needed. One option is to add a third, non–cross-resistant drug to carboplatin and paclitaxel, as we have done in this study. Specifically, we tested whether sequential administration of topotecan would improve the efficacy (i.e., overall survival, overall response, and progression-free survival) of carboplatin and paclitaxel. We found that it did not. We also found that the sequential addition of topotecan to carboplatin–paclitaxel induced higher rates of hematologic toxic effects and infections, requiring statistically significantly more supportive care (Table 2). This higher toxicity is consistent with the results of earlier phase II studies *(16,17)*. The clinical consequences of the higher toxicity rates in the TC-Top arm were acceptable. For example, the rate of grade 3 or 4 febrile neutropenia in the TC-Top arm was not statistically significantly different from the rate in the TC arm (3.3% versus 3.1%) and, although the rate of grade 3 or 4 infection was statistically significantly higher in the TC-Top arm than in the TC arm (5.1% versus 2.7%), the levels in both arms were acceptable. Also, global quality-of-life scores were not worse in those treated with topotecan.

Even if sequential topotecan had improved survival after carboplatin–paclitaxel, the resulting hazard ratio reduction would probably have been less than 14% (equivalent to the lower 95% confidence limit of the estimated hazard ratio of 0.86). There are several possible reasons why we observed no improvement in

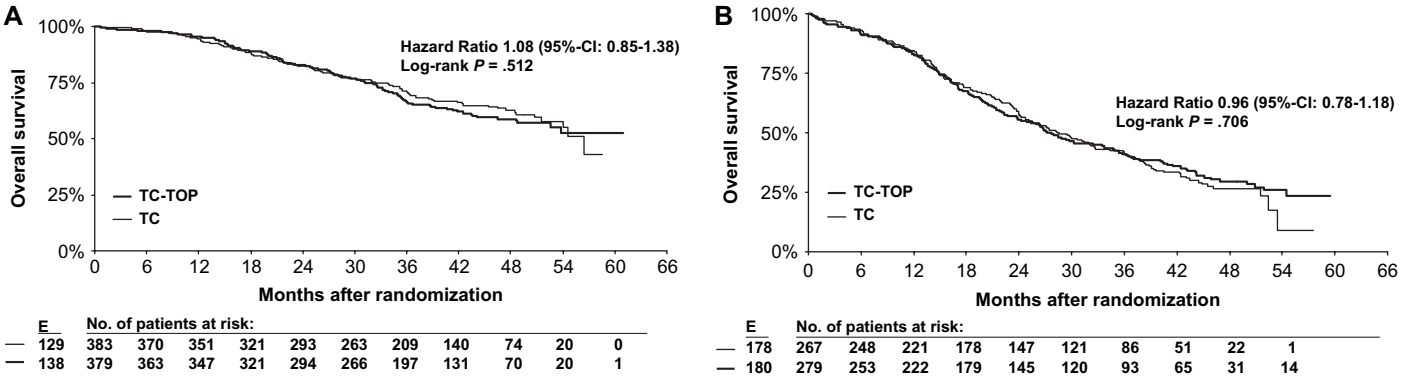

Fig. 3. Kaplan–Meier curves for overall survival for all randomly assigned patients in each stratum by treatment group. (**A**) Stratum 1. (**B**) Stratum 2. Stratum 1 included patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB–IIIC disease and residual tumors 1 cm and smaller. Stratum 2 included patients with FIGO stage IV disease or stage IIB–IIIC disease with residual tumors larger than 1 cm. TC = carboplatin–paclitaxel; TC-TOP = carboplatin–paclitaxel–topotecan; TOP = topotecan; E = number of events; CI = confidence interval.

survival among the TC-Top arm. First, this lack of improvement could be due to patients in the TC arm receiving treatment with topotecan, maybe without having progressed. This possibility is unlikely because only 26 (2%) of the enrolled patients were treated without evidence of disease progression. Furthermore, only a few patients (9%) were treated with topotecan after progression, although there was a difference of 10% (TC-arm, 14%; versus TC-Top arm, 4%) between treatment arms. Postrecurrence therapy is known to have an impact on overall survival; nevertheless, it is not now possible to standardize postrecurrence/progression therapy *(32,33)*. Also, these different percentages of topotecan use might be of minor relevance because the median progression-free and overall survival times reported here are in the same range of results achieved with carboplatin–paclitaxel in other studies *(4,6)*. Another limitation of this study might be that 19 patients (1.5%) never started treatment and 157 patients (12%) stopped treatment earlier than intended, mainly because of progressive disease. It can be argued that a shorter treatment period and a lower total dose of carboplatin–paclitaxel might have resulted in shorter survival. Furthermore, it is possible that patients who progressed under carboplatin–paclitaxel treatment and thus went off treatment might have profited from topotecan treatment. However, we repeated the analysis on a per-protocol basis and obtained results that agreed with those obtained in the intention-to-treat analysis. Moreover, we took this dropout rate into consideration when calculating the sample size. According to the Third International Ovarian Cancer Consensus Conference, the standard arm of our trial was appropriate in terms of drugs and dosages *(33)*.

Our results are in agreement with those of the MITO-1 study, which used topotecan as consolidation treatment for ovarian cancer after carboplatin–paclitaxel *(34)*. However, there were major differences between these studies. For example, we used a triple-drug regimen in a sequential way (i.e., up-front randomization), whereas the MITO-1 study was a consolidation study (i.e., randomization after response to six cycles of carboplatin–paclitaxel). The two studies used different dosages of topotecan: 1.25 mg/m^2 on cycle days 1–5 (our study) versus 1.5 mg/m^2 on cycle days 1–5 (MITO-1 study)—as well as different primary endpoints—overall survival (our study) versus progression-free survival (MITO-1 study). Despite these differences, topotecan did not improve the efficacy of six cycles carboplatin–paclitaxel in either setting.

This is the first and, to our knowledge, only phase III study to investigate topotecan in a sequential triple-drug regimen for first-line therapy of advanced ovarian cancer. Interpretation of the negative results of this trial should be limited to the sequential use of topotecan. Other investigators have applied a doublet combination approach by adding topotecan to platinum for four cycles followed by four cycles of platinum–paclitaxel *(10,35)*. This approach may result in superior efficacy, considering that preclinical models have suggested an advantage for the combination of topotecan and platinum due to the inhibition of DNA synthetic pathways involved in the repair of platinum–DNA adducts *(36)*. Because increased toxicity makes it unfeasible to treat patients with a simultaneous drug regimen of carboplatin, paclitaxel, and topotecan, the above-mentioned sequential doublet approach might be superior to the sequential single agent used in this study. Results of these two other prospective randomized phase III studies may help our understanding of the role of topotecan as part of first-line therapy of advanced ovarian cancer. Both studies have recently completed accrual and results are expected within the next few years. In the meantime, in accordance with the results of the 2004 consensus statement on the management of ovarian cancer of the Third International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference *(7)*, carboplatin–paclitaxel remains the standard of care for patients with advanced ovarian cancer.

Appendix

The following physicians or centers (listed in alphabetical order with respect to city) enrolled three or more patients.

AGO-OVAR (Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom): Aachen (W. Rath); Aalen (K. von Maillot); Amberg (A. Scharl); Aschaffenburg (E. Schlicht); Aue/Schlema (J. Dietel); Bad Hersfeld (M. Bahner); Baden-Baden (C. Villena); Balingen (T. J. Horvath); (Bayreuth) A. H. Tulusan; Berlin (M. Abou-Dakn, J.-U. Blohmer, A. Hecht, G. Morack, J. Potenberg, U. Torsten); Bielefeld (H. J. Weh); Bonn (B. Brückner); Bremen (W. Schröder); Bruchsal (J. Wacker); Chemnitz (K. Renziehausen); Cloppenburg (A. Feldmann); Delmenhorst (W. Knapp); Dresden (B. Richter); Duisburg (U. Hurst, Ch. Werner); Düsseldorf (W. Meier, U. Nitz); Ebersberg (C. Höß); Elmshorn (T. Dewitz); Erfurt (G. Dötsch, Ch. Müller); Esslingen (H. Mickan); Frankfurt/M. (S. Costa, V. Möbus, D. Wernicke); Frankfurt/O. (H. Seik); Freiburg (D. Kieback); Freudenstadt (J. Schulze-Tollert); Fulda (B. Stitz); Gelsenkirchen (M. Stibora); Georgsmarienhütte (M. Hoedemaker); Gera (M. Kröner); Göttingen (T. Krauß); Graz/Österreich (E. Petru); Greifswald (J. Quaas); Hagen (E. Schneller); Halberstadt (K. Fritz); Halle/S. (H.-G. Strauß); Hamburg (H. Daneschumand, F. Jänicke, P. Schmidt-Rhode); Hanau (H. H. Zippel); Hannover (H.-J. Lück); Heilbad Heiligenstadt (K.-D. Ketscher); Henstedt-Ulzburg (T. Zeiser); Herzberg am Harz (W. Herchenhein); Homburg/S. (W. Schmidt); Jena (A. Schneider); Karlsruhe (G. Deutsch, A. Stähle); Kassel (H. Urbanczyk); Kiel (J. Pfisterer); Köln (Ch. Kurbacher, W. Maurer, S. Sünter); Kulmbach (D. Hägele); Lahr (A. Göppinger); Langen (R. Schuhmann); Leonberg (M. Kuglin); Lich (U. Kullmer); Lindau (E.-D. Mauch); Lübeck (M. Löning); Ludwigshafen (M. Grillo, A. Schenk); Lüneburg (H.-J. Bettex); Magdeburg (B. Schindler, W. Weise); Mainz (U. Spettel-Stauder); Mannheim (F. Melchert); Marburg (K.-D. Schulz); München (W. Eiermann, R. Kimmig, W. Kuhn, H. Sommer); Münster (C. Jackisch); Neunkirchen (G.-P. Breitbach); Oberhausen (R. Göbel); Offenburg (D. Schwörer); Osnabrück (M. Butterwegge); Paderborn (W. Meinerz); Peine (A. Niesel); Plauen (P. Richter); Potsdam (F. Dreßler); Quedlinburg (O. Boldt); Rheinfelden (I. Küpfer); Riesa (M. Lange); Rosenheim (T. Beck); Rostock (K. Friese, G. Scharlau); Rotenburg (W.) (J. Neumann); Salzgitter-Bad (D. Scharnke); Siegen (F. Lauber, M. Losch); Sigmaringen (J. Meyer-Grohbrügge); Solingen (V. Jovanovic); Stadthagen (J. Feltz-Süßenbach); Stuttgart (T. Rau-Horn); Torgau (G. Göretzlehner); Tübingen (U. Wagner); Ulm (R. Kreienberg); Vechta (J. Diers); Waiblingen (C. Karg); Wiesbaden (A. du Bois, G. Hofmann); Wittenberg (H. Schröder); Wolfsburg (G. Bothmann); Würzburg (D. Kranzfelder).

GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens): Ales (J. Cretin); Angers (A. Lortholoary); Beauvais (J.-L. Dutel); Bordeaux (N. Dohollou); Bourg-en-Bresse (H. Orfeuvre); Brive (B. Leduc); Colmar (J.-C. Barats); Dijon (B. Coudert, M. Flesch); Ermont (C. Boaziz); Grenoble (M. Mousseau); Le Chesnay (D. Mayeur); Le Mans (M. Combe); Lyon (J.-P. Guastalla, J.-D. Tigaud); Marseille (A. Nicoara); Meaux (G. Netter-Pinon); Montbéliard (J. Plaza); Nice (J.-M. Ferrero); Orleans (V. Lucas); Paris (L. Chauvenet); Poitiers (H. Bourgeois); Roanne (M.-C. Gouttebel); Saint Brieuc (A.-C. Hardy-Bessard); Saint Cloud (A. Goupil); Suresnes (L. Mignot); Thonon (J. Salvat); Valence (H. Barletta, P.-Y. Peaud); Vandoeuvre-Les-Nancy (B. Weber).

References

(1) McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6.

(2) Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699–708.

(3) Piccart MJ, Bertelsen K, Stuart G, Cassidy J, Mangioni C, Simonsen E, et al. Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. Int J Gynecol Cancer 2003;13(Suppl 2):144–8.

(4) du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320–9.

(5) Neijt JP, Engelholm SA, Tuxen MK, Sorensen PG, Hansen M, Sessa C, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol 2000;18:3084–92.

(6) Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al. 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. J Clin Oncol 2003;21:3194–200.

(7) du Bois A, Quinn M, Thigpen T, Vermorken J, Avall-Lundqvist E, Bookmann M, et al. 2004 Consensus Statements on the Management of Ovarian Cancer—Final Document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). Ann Oncol 2005;16(Suppl 8):viii7–12.

(8) du Bois A, Weber B, Rochon J, Meier W, Goupil A, Olbricht A, et al. Addition of epirubicin as third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol 2006;24:1127–35.

(9) Kristensen GB, Vergote I, Eisenhauer E, Baekelandt M, Stuart G, Avall-Lundquist E, et al. First line treatment of ovarian/tubal/peritoneal cancer FIGO stage IIb-IV with paclitaxel/carboplatin with or without epirubicin (TEC vs TC). A Gynecologic Cancer Intergroup study of the NSGO, EORTC GCG, and NCIC CTG. Results on progression-free survival. J Clin Oncol 2004;22:5003.

(10) Copeland LJ, Bookman M, Trimble E. Clinical trials of newer regimens for treating ovarian cancer: the rationale for Gynecologic Oncology Group Protocol GOG 182-ICON5. Gynecol Oncol 2003;90(2 Pt 2):1–7.

(11) Gore M, ten Bokkel Huinink W, Carmichael J, Gordon A, Davidson N, Coleman R, et al. Clinical evidence for topotecan-paclitaxel non-cross-resistance in ovarian cancer. J Clin Oncol 2001;19:1893–900.

(12) Ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183–93.

(13) Ten Bokkel Huinink W, Lane SR, Ross GA. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Ann Oncol 2004;15:100–3.

(14) Gordon A, Fleagle J, Guthrie D, Parkin D, Gore M, Lacave A. Recurrent Epithelial Ovarian Carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312–22.

(15) Gordon A, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 2004;95:1–8.

(16) Chan S, Carmichael J, Ross G, Wheathly A, Howell J, Patterson J. Sequential hycamtin following carboplatin and paclitaxel in advanced ovarian cancer. Proc ASCO 1999;18:1436.

(17) Bolis G, Scarfone G, Villa A, Parazzini F. Phase II trial of topotecan, carboplatin, and paclitaxel as front-line therapy in suboptimal advanced ovarian cancer. Gynecol Oncol 2001;81:331–3.

(18) Pfisterer J, Lortholary A, Kimmig R, Weber B, du Bois A, Bourgeois H, et al. Paclitaxel/carboplatin (TC) vs. paclitaxel/carboplatin followed by topotecan (TC-Top) in first-line treatment of ovarian cancer FIGO stages IIb-IV. Interim results of a Gynecologic Cancer Intergroup phase III trial of the AGO Ovarian Cancer Study Group and GINECO. Proc ASCO 2003;22:1793.

(19) Pfisterer J, Weber B, du Bois A, Lortholary A, Schade-Brittinger C, Wagner U, et al. Paclitaxel/carboplatin (TC) vs. paclitaxel/carboplatin followed by topotecan (Top) in first-line treatment of ovarian cancer FIGO stages IIB-IV. Mature results of a Gynecologic Cancer Intergroup phase III trial of the AGO OVAR and GINECO. J Clin Oncol 2005;23:5007.

(20) International Federation of Gynecology and Obstetrics. Changing in definitions of clinical staging for carcinoma of the cervix and ovary. Am J Obstet Gynecol 1987;156:263–4.

(21) FIGO Grading System. Acta Obstet Gynecol Scand 1971;50:1–7.

(22) Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. In: V. De Vita, S. Hellmann, and S. Rosenberg, editors. Cancer: principles and practice of oncology. Philadelphia (PA): Lippincott; 1984. p. 536.

(23) Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.

(24) Jelliffe RW. Creatinine clearance: bedsite estimate. Ann Intern Med 1973;79:604–5.

(25) National Cancer Institute. Cancer Therapy Evaluation Program: Common Toxicity Criteria. Available from: http://ctep.cancer.gov/reporting/ctc.html. [Last accessed: May 24, 2006].

(26) Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, et al. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000;47:13–47.

(27) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

(28) Cull A, Howat S, Greimel E, Waldenstrom AC, Arraras J, Kudelka A, et al. Development of a European Organization for Research and Treatment of Cancer questionnaire module to assess the quality of life of ovarian cancer patients in clinical trials: a progress report. Eur J Cancer 2001;37:47–53.

(29) Greimel E, Bottomley A, Cull A, Waldenstrom AC, Arraras J, Chauvenet L, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 2003;39:1402–08. [Published erratum appears in Eur J Cancer 2003;39:2570.]

(30) Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M; on behalf of the EORTC Quality of Life Study Group: The EORTC QLQ-C30 Scoring Manual. 2nd ed. Brussels (Belgium): European Organization for Research and Treatment of Cancer; 1999.

(31) World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization. 1979 (Offset Publication No. 48). Available from: http://whqlibdoc.who.int/publications/9241700483.pdf. [Last accessed: May 24, 2006.]

(32) Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099–106.

(33) Thigpen T, Stuart G, du Bois A, Friedlander M, Fujiwara K, Guastalla JP, et al. Clinical trials in ovarian carcinoma: requirements for standard approaches and regimens. Ann Oncol 2005;16(suppl 8):viii13–19.

(34) De Placido S, Scambia G, Di Vagno G, Naglieri E, Vernaglia Lombardi A, Biamonte R, et al. Topotecan compared with no therapy after response to surgery and carboplatin/paclitaxel in patients with ovarian cancer: Multicenter Italian Trials in Ovarian Cancer (MITO-1) randomized study. J Clin Oncol 2004;22:2635–42.

(35) Current Site Committee and Supportive Care Trials. Available from: http://www.ctg.queensu.ca/public/Clinical_Trials/public_ph_3_trial_summary.html#OV16. [Last accessed: May 24, 2006.]

(36) Chou TC, Motzer RJ, Tong Y, Bosl GJ. Computerized quantitation of synergism and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design. J Natl Cancer Inst 1994;86:1517–24.

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