Reprinted from THE JOURNAL OF CLINICAL ONCOLOGY
Vol. 17, No. 1 January, 1999
Published by Lippincott Williams & Wilkins

First-Line Chemotherapy With Epirubicin, Paclitaxel, and Carboplatin for Advanced Ovarian Cancer: A Phase I/II Study of the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group

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Purpose: **Despite the progress that has been achieved over the years, survival rates in patients with advanced ovarian cancer are still disappointing. New methods to improve the efficiency of first-line chemotherapy are warranted. One method to improve results is to add more non–cross-resistant drugs to platinum-paclitaxel combination regimens. Anthracyclines are among the candidates for incorporation as the "third drug" into first-line regimens for advanced ovarian cancer.**

Patients and Methods: **We performed a phase I/II trial with escalating doses of epirubicin (60, 75, and 90 mg/m^2) combined with fixed doses of paclitaxel and carboplatin in 27 previously untreated patients with advanced gynecologic malignancies.**

Results: **Dose-limiting toxicity occurred at dose level 2 (75 mg/m^2 epirubicin) and consisted of myelosuppression (neutropenia, thrombocytopenia). No dose-limiting, nonhematologic toxicities were observed. The maximum tolerable dose was epirubicin 60 mg/m^2 (E) combined with a 3-hour infusion of paclitaxel 175 mg/m^2 (T) and carboplatin AUC 5 (Carbo). Preliminary analysis indicated promising activity against ovarian cancer.**

Conclusion: **The three-drug combination ET-Carbo, given according to the outlined dose and schedule, should be considered for further phase III evaluation. A randomized German-French intergroup trial comparing ET-Carbo with carboplatin-paclitaxel has already been initiated.**

J Clin Oncol 17:46-51. ***© 1999 by American Society of Clinical Oncology.***

SINCE THE PUBLICATION OF Gynecologic Oncology Group (GOG) protocol no. 111 in early 1996,[1] the combination regimen of cisplatin and paclitaxel has been adopted as a new standard first-line treatment for advanced ovarian cancer. Several attempts have been made to optimize this regimen, which consists of cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 given as a 24-hour infusion. A Canadian-European intergroup study that used paclitaxel 175 mg/m^2 given over 3 hours in combination with cisplatin 75 mg/m^2 has principally confirmed the results of GOG no. 111 by showing a superior effectiveness of the new combination when compared with the old standard regimen of cisplatin and cyclophosphamide.[2] Further efforts were undertaken to amend the armamentarium of platinum-taxan combinations for the treatment of ovarian cancer by substituting cisplatin with carboplatin. At least three prospectively randomized trials comparing cisplatin/paclitaxel with carboplatin/paclitaxel were initiated, one in the United States (GOG no. 158) and two in Europe (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] protocol *OVAR-3* and a Dutch-Danish study). Interim analysis of the latter two studies suggested similar efficacy when carboplatin/paclitaxel was compared with cisplatin/paclitaxel,[3,4] although long-term survival data are still needed.

One option for achieving further progress in the first-line treatment of advanced ovarian cancer might be the addition of non–cross-resistant drugs to the two-drug combination of platinum and paclitaxel. Anthracyclines are among the candidates for the "third drug." Three meta-analyses showed a survival benefit for platinum-anthracycline–based combinations when compared with platinum-based combinations without anthracyclines.[5-7] Furthermore, both doxorubicin (as a liposomal formulation) and epirubicin, a doxorubicin analog, have shown activity as second-line treatment even after prior platinum (and in some patients, paclitaxel) first-line chemotherapy.[8,9]

In our phase I/II study, we evaluated the maximum-tolerated dose, safety, and feasibility of a three-drug regimen containing an anthracycline (ie, epirubicin) in combination with carboplatin and paclitaxel in previously untreated patients with gynecologic cancers. Epirubicin was selected among the available anthracyclines because it has shown less cardiotoxicity than doxorubicin when combined with cisplatin in a randomized trial.[10] The same observations have been reported when epirubicin or doxorubicin were combined with paclitaxel in phase II breast cancer trials.[11-14]

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Submitted June 26, 1998; September 14, 1998.

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0732-183X/99/1701-0046$3.00/0

PATIENTS AND METHODS

This study was conducted according to the Good Clinical Practice guidelines. Approval from ethics committees was gained at every institution, and each patient gave written informed consent. Inclusion criteria were histologically confirmed epithelial ovarian cancer, primary peritoneal adenocarcinoma, or papillary-serous endometrial carcinoma, age of consent, Eastern Cooperative Oncology Group performance status of 2 or better, adequate bone-marrow function (absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L), and adequate renal and hepatic function (creatinine and bilirubin ≤ 1.25 times the upper limit of normal). Patients were ineligible if they had prior malignancies (excluding nonmelanomatous skin cancer), prior chemotherapy or radiotherapy, a history of atrial or ventricular arrhythmias, congestive heart failure or a history of myocardial infarction, pre-existing motor or sensory neurotoxicity, active infection, bowel obstruction, or mental disorders.

Chemotherapy consisted of escalating doses of epirubicin, starting at 60 mg/m^2 in dose level 1, with an escalation of 15 mg/m^2 in each higher dose level (ie, 60, 75, and 90 mg/m^2), followed by fixed doses of paclitaxel 175 mg/m^2 given as a 3-hour infusion and carboplatin AUC 5. All three drugs were administered on day 1, one directly after another, and cycles were repeated every 21 days. This sequence was chosen because epirubicin preceding paclitaxel has shown excellent tolerability (especially no cardiotoxicity) in our phase I/II breast cancer trial,[13] and carboplatin given after paclitaxel has shown better tolerability than vice versa in our phase I/II ovarian trial.[17] Carboplatin dose was calculated as AUC according to the Calvert formula.[15] The glomerular filtration rate was estimated according to the Jeliffe formula.[16] Epirubicin was diluted in 250 mL of glucose 5% and infused over the course of 30 minutes. Paclitaxel was diluted in 500 mL of 0.9% saline and infused over the course of 3 hours. Carboplatin was diluted in 500 mL of glucose 5% and infused over the course of 30 to 60 minutes. The premedication schedule had been evaluated before in our phase I/II trial with carboplatin-paclitaxel[17] and consisted of single-dose dexamethasone 20 mg, ondansetron 8 mg, clemastine 2 mg, and ranitidine 50 mg given directly before chemotherapy. Blood counts were monitored during each course, once in the first week and twice in the second and third weeks. Electrocardiogram tracing was performed before study entry and after treatment completion. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.[18] No primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was allowed. The maximum-tolerated dose (MTD) was defined as one dose level below the dose level in which at least two of eight patients developed dose-limiting toxicity. Dose-limiting toxicity (DLT) was defined as (1) absolute neutrophil count (ANC) less than 0.5×10^9/L lasting for more than 7 days, (2) ANC less than 0.1×10^9/L lasting for more than 3 days, (3) febrile neutropenia, (4) grade 4 thrombocytopenia, and (5) clinically relevant nonhematologic toxicity of grade 3 or higher. Re-treatment was delayed until thrombocyte counts had reached 100×10^9/L and the ANC was 1.5×10^9/L or higher. Patients were taken out of the study if the treatment interval exceeded 42 days. Dose-limiting toxicity was evaluated over the first three consecutive courses per patient. Patients were enrolled in the next higher dose level only in the absence of DLT within the first course in at least seven of eight patients in the preceding dose level. After the MTD level was defined, at least eight additional patients had to be treated for confirmation at this dose level. Maximum-tolerated dose was only accepted if fewer than four of 16 patients experienced DLT within the first three consecutive courses. Treatment continued in patients who experienced DLT, but doses had to be reduced to the next lower dose level in subsequent courses. Dose reductions for patients treated at level 1 were epirubicin 45 mg/m^2 (level -1) and cessation of epirubici (level -2). Paclitaxel and carboplatin doses were kept unchange during the course of the whole study.

Bidimensionally measurable tumors were not mandatory for inclu sion, but patients with ovarian cancer who presented with measurabl tumors were evaluated for response. Gynecologic clinical examination were performed before each course. Imaging techniques appropriate fc tumor measurement were performed every other course. Responses tha were primarily detected by clinical examination or ultrasound had to b verified by computed tomographic scan. Response was defined accorc ing to the International Union Against Cancer's criteria.[19]

RESULTS

From June 1997 to October 1997, twenty-seven patient were recruited. One patient was found to be ineligibl because she had received one prior course of chemotherap consisting of carboplatin, paclitaxel, and ifosfamide. Th remaining 26 patients received 140 chemotherapy course Patient characteristics were well balanced in all dose level (Table 1). The majority of patients had ovarian cancer, th median age was 58 years, and the median glomerula filtration rate was 83 mL/min (range, 55 to 115 mL/min Eighteen of the 21 patients with ovarian cancer wer assessable for efficacy (two patients received only on course and one patient was not evaluated for response); a courses were assessable for toxicity.

Dose Escalation and Dose-Limiting Toxicity

Eight patients were entered onto dose level 1 (epirubici 60 mg/m^2); of these eight patients, only one patient (patier no. 1) developed DLT with neutropenia grade 4 lastin longer than 7 days, thus allowing further dose escalation. A additional eight patients were entered onto level 2 (epirubi

Table 1. Patient Characteristics

	ET-Carbo	
	Level 1*	Level 2†
Patients	18 (8 + 10)	8
Courses	92	48
Age, years		
Median	56	62
Range	40-67	49-71
GFR, mL/min		
Median	83	83
Range	62-115	55-11
Diagnosis		
Ovarian cancer	13	8
Peritoneal cancer	4	—
Endometrial cancer	1	—

Abbreviations: ET-Carbo, epirubicin, paclitaxel, and carboplatin; GF glomerular filtration rate.

*Level 1: epirubicin 60 mg/m^2, paclitaxel 175 mg/m^2, and carboplat AUC 5.

†Level 2: epirubicin 75 mg/m^2, paclitaxel 175 mg/m^2, and carboplat AUC 5.

cin 75 mg/m^2), and of this group, three patients developed DLT, with neutropenia grade 4 lasting longer than 7 days in two patients (patient nos. 9 and 13) and neutropenic fever in one patient (patient no. 14). Further dose escalation was stopped when three of eight patients developed DLT in the first treatment course of dose level 2. In the first three treatment courses, two patients on dose level 1 developed DLT with neutropenia grade 4 for more than 7 days (patient no. 1, course 1), and one patient developed thrombocytopenia grade 4 (patient no. 3, course 3). Four of the eight patients on dose level 2 experienced DLT during their first three treatment courses had neutropenia grade 4 for more than 7 days (patient no. 9, course 1; patient no. 13, courses 1 + 3; patient no. 10, course 3) or neutropenic fever (patient no. 14, course 1; patient no. 10, course 2). An additional 10 patients were enrolled onto dose level 1 for confirmation of the MTD. No further toxicities classified as DLT were observed within the first three treatment courses in these patients. Therefore, dose level 1, consisting of epirubicin 60 mg/m^2 followed by paclitaxel 175 mg/m^2 and carboplatin AUC 5, was regarded as the MTD.

Toxicity

Hematologic toxicity consisted mainly of grade 4 neutropenia, which occurred in 52% and 60% of courses in dose level 1 and level 2, respectively. The rather small difference between these two dose levels was due, at least in part, to dose reduction, which occurred in five of the eight patients on dose level 2 during their treatment. When only the worst course is considered, 62.5% and 87.5% of patients experienced grade 4 neutropenia on dose levels 1 and 2, respectively. Thrombocytopenia grade 3/4 was observed in 13% and 23% of courses in dose levels 1 and 2, respectively. Again, the difference between the two dose levels was more pronounced when a worst-course analysis was performed. Twenty-nine percent and 75% of patients experienced at least one course with thrombocytopenia grade 3/4 while on dose levels 1 and 2, respectively. Anemia was not of major clinical relevance (Table 2). Secondary prophylaxis with G-CSF and therapeutic or prophylactic treatment with antibiotics occurred more commonly in dose level 2. Severe nonhematologic toxicities of clinical relevance concerning DLT were not observed in either of the dose levels. Only one patient reported grade 3 nausea, and one other patient experienced a short period of severe hypersensitivity grade 3 with bronchial obstruction. This patient recovered completely after the paclitaxel infusion was stopped. She was rechallenged some hours later and completed treatment with slower infusions of paclitaxel. Grade 1/2 nonhematologic toxicities did not differ between dose levels 1 and 2; details for the whole study population are listed in Table 3.

Table 2. Hematologic Toxicity

	ET-Carbo			
	Level 1 (% of 92 courses)		Level 2 (% of 48 courses)	
	Grade 3*	Grade 4	Grade 3	Grade 4
Anemia	2	1	2	2
Thrombocytopenia	10	3	23	—
Leukopenia	38	6	33	7
Neutropenia	16	52	19	60
Secondary G-CSF	2		15	
Antibiotics	1		5	

Abbreviation: ET-Carbo, epirubicin, paclitaxel, and carboplatin.

*Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

Actual Dose

Fourteen of 16 patients on dose level 1 completed six treatment courses, and two patients received only one course each. One patient refused further participation in the study after one treatment course, and another patient was taken out of the study after her biliary duct stent occluded and subsequently underwent surgery for this reason. Dose reduction was necessary in four patients after course 1 (one patient), course 3 (one patient), and course 4 (two patients). Treatment delay of more than 1 week was observed in eight (8.7%) of 92 courses. All eight patients included on dose level 2 received six treatment courses, but only three of the eight patients completed treatment at the starting dose. Five patients needed dose reduction to dose level 1; three of these five patients received further dose reductions to level −1,

Table 3. Nonhematologic Toxicity of Epirubicin, Paclitaxel, and Carboplatin in 26 Patients With 140 Courses

	NCI CTC Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Emesis	42	27	—	—
Nausea	42	38	4	NA
Diarrhea/constipation	23	27	—	—
Stomatitis	38	15	—	—
Infection	15	15	—	—
Myalgia	23	15	—	—
Pain	23	—	—	—
Neurotoxicity, PNS	46	19	—	—
Neurotoxicity, CNS	11	—	—	—
Ototoxicity	8	—	—	—
Alopecia	8	92	NA	NA
Edema	8	—	—	—
Hypersensitivity	11	—	4	—
Arrhythmia	11	—	—	—

NOTE. The worst course per patient was counted.

Abbreviations: NCI CTC, National Cancer Institute Common Toxicity Criteria; NA, not applicable.

and two of these three patients who experienced DLT, despite two dose reductions, received treatment at level −2 in subsequent courses. Treatment intervals exceeded 28 days in five (10.4%) of 48 courses in level 2. Dose-intensity over the whole treatment period was higher in dose level 1 patients than in patients who started with dose level 2.

Efficacy

Seven of 21 patients with ovarian cancer had bidimensionally measurable disease, and six of the seven were assessable for clinical response. Four patients achieved a complete response, one patient showed a partial response, and one patient had tumor progression. One patient refused further participation in the study after her first course and was not evaluated for response. Fourteen patients with ovarian cancer had nonmeasurable disease at study entry. Ten patients had no evidence of disease after completion of treatment, and three of these 10 patients underwent second-look surgery, which showed two pathologically confirmed complete responses and one partial response with microscopic tumor residuals. One patient in this group experienced tumor progression, and three patients were found to be unassessable. Response was not evaluated in patients with tumors others than epithelial ovarian carcinoma.

DISCUSSION

Despite the progress that had been achieved by the incorporation of paclitaxel into first-line treatment of advanced ovarian cancer, survival rates are still somewhat disappointing. Eventually, the majority of patients will develop secondary drug-resistant recurrences and die of their disease. Therefore, further efforts to improve efficacy of first-line chemotherapy in ovarian cancer are clearly warranted. One method to improve results is the addition of other drugs that are regarded as not completely cross-resistant to platinum-paclitaxel combination regimens. Among other drugs, anthracyclines are candidates for incorporation as the "third drug" into first-line regimens for advanced ovarian cancer. Results from meta-analyses have suggested that anthracyclines, when added to platinum-cyclophosphamide regimens, offer some benefit in regard to long-term survival.[5-7] Today, it is unknown whether this additional impact of anthracyclines is maintained when anthracycline is combined with the new standard regimen of platinum and paclitaxel. This study was undertaken to develop a feasible three-drug regimen that would offer the opportunity to compare platinum-paclitaxel with a three-drug combination of platinum plus paclitaxel plus an anthracycline in future randomized phase III trials. These studies should help to clarify the role of anthracyclines in ovarian cancer.

At least nine groups (including the AGO group) hav evaluated anthracycline-containing three-drug regimens f the treatment of gynecologic malignancies.[20-27] Three grou used doxorubicin and six groups chose epirubicin as t anthracycline.

Epirubicin was combined with cisplatin and paclitaxel three studies and with paclitaxel and carboplatin in thr other studies (Table 4). An Italian group reached MTD wi epirubicin 75 mg/m^2 in combination with paclitaxel 1 mg/m^2 and carboplatin AUC 6.[26] This group chose 4-we intervals; in contrast, we used 3-week intervals and th achieved a slightly higher dose-intensity, although we us lower single doses of epirubicin (60 mg/m^2) and carboplat (AUC 5) in each course. The second trial, which w presented as an abstract by a Scandinavian group, used t same paclitaxel dose as we did but a slightly high epirubicin dose of 75 mg/m^2.[27] These additional 15 mg/m of the anthracycline were traded for a lower carboplatin do of AUC 4. Neither the use of cisplatin instead of carbopl tin[23-25] nor the use of doxorubicin instead of epirubicin[20- resulted in higher anthracycline doses.

The major dose-limiting toxicity reported from all studi was myelosuppression (mainly neutropenia). Granulocyte colon stimulating factor seemed to have only minor impact on t maximum-tolerated doses. Six groups used prophylactic G-C treatment in all patients, but maximum-tolerated doses did n exceed those reported from studies in which G-CSF was n used (Table 4). This observation corresponds to an earli report indicating that G-CSF did not allow dose escalation carboplatin-paclitaxel combination chemotherapy.[28]

Overall, maximum-tolerated doses were very similar all studies that used paclitaxel 135 to 175 mg/m^2 given 3-hour infusions. The exception was one study that us 24-hour infusions of paclitaxel,[20] cisplatin 50 to 75 mg/m^2 carboplatin AUC 5 to 7, and doxorubicin 30 to 50 mg/m^2 epirubicin 50–75 mg/m^2. Only one study[25] reported high doses for all three drugs, but a substantial proportion patients experienced nonhematologic toxicities, includi cardiotoxicity. In contrast, no severe nonhematologic toxic ties were observed in our trial, making the present maximu tolerable dose feasible for phase III studies.

Some groups, as well as this study, have reported prelim nary efficacy data for the three-drug regimens consisting taxanes, platinum, and an anthracycline.[20,21,23,24,26,27] Ov all response rates range from 63% to 100% of assessab patients, with complete response rates of 40% to 89%. The data should be interpreted very cautiously, because ea study included only few patients and response rates a based on a total sample of only 135 patients enrolled on seven phase I/II and phase II trials. In addition, two of the

Table 4. Phase I/II Studies of Three-Drug Combinations Containing Platinum, Paclitaxel, and Anthracyclines in Patients With Gynecologic Malignancies

Anthracycline Doxorubicin (mg/m²)	Taxane Paclitaxel (mg/m²) (hours)	Platinum Cisplatin (mg/m²)	G-CSF	MTD	No. of Patients (courses)	DLT*	Site of Primary Tumor	Ref.
30 → 40	135 (24)	75	+	30/135/75	9 (NR)	Thrombocytopenia Nephrotoxicity	Ovary	20
		75			8	Neutropenia	Ovary	21
50	175 (3)		+	NA	(82)	Infections	Gynecol‡	
		AUC7†			8			
45	60 → 250 (3)	60	+	45/160/60	70 (265)	Neutropenic fever Neuromuscular tox.	Gynecol§	22
Epirubicin (mg/m²)	Paclitaxel (mg/m²) (hours)	Cisplatin (mg/m²)						
70	175 (3)	50	NR	NA	15 (65)	Neutropenia Febrile neutropenia	Uterus	23
50	135 (3)	75	+	NA	40 (NR)	Neutropenia Febrile neutropenia	Ovary	24
70 → 110	135 → 195 (3)	100	+	NR	30 (NR)	Emesis, stomatitis Cardio-, neurotox.	Ovary	25
Epirubicin (mg/m²)	Paclitaxel (mg/m²) (hours)	Carboplatin (AUC)						
60 → 90	175 (3) q 28 d	6	NR	75/175/AUC 6	34 (129)	Neutropenia Febrile neutropenia Thrombocytopenia	Ovary	26
75	175 (3)	4	–	NA	15 (65)	Neutropenia	Ovary	27
60 → 75	175 (3)	5	–	60/175/AUC 5	26 (140)	Neutropenia Febrile neutropenia Thrombocytopenia	Ovary Gynecol‖	This study

Abbreviations: NR, not reported; NA, not applicable.
*If DLT was not reported, main grade 3/4 toxicities are given (phase II trials).
†Carboplatin.
‡Mixed mullerian, peritoneal, celomic, fallopian tube carcinoma.
§Gynecologic cancer except ovarian carcinoma.
‖Peritoneal adenocarcinoma (4) and endometrial cancer (1).

trials included patients with gynecologic malignancies other than epithelial ovarian cancer, thereby making results incomparable. Nevertheless, the anthracycline-paclitaxel-platinum combination showed promising activity against ovarian cancer; therefore, further evaluation in phase III trials is justified. On the basis of results of our phase I/II trial, a German-French randomized phase III intergroup trial was initiated in November 1997. This trial is comparing epirubicin-paclitaxel-carboplatin with carboplatin-paclitaxel. By November 1998, 600 of the 800 planned patients had already entered onto this trial. Investigators expect to complete recruitment in 1999.

ACKNOWLEDGMENT

We thank the study secretaries (T. Hirsjärvi, G. Elser, and M. Polzin) for help with the data management and P. Schantl, C. Biberger, and B. Kirchherr for outfield data monitoring. Study medication was provided by Bristol-Myers-Squibb (paclitaxel and carboplatin) and Pharmacia-Upjohn (epirubicin).

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