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Paclitaxel 175 or 225 mg per Meters Squared With Carboplatin in Advanced Ovarian Cancer: A Randomized Trial

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To analyze the effect of different doses of paclitaxel with fixed doses of carboplatin in the treatment of ovarian cancer.

Patients and Methods
Patients with histologically confirmed epithelial ovarian cancer, International Federation of Gynecology and Obstetrics stages IIB to IV, were eligible for this randomized, multicenter study. Women were randomly assigned to treatment with (1) carboplatin at the dose (in milligrams) corresponding to the following formula: target area under the free carboplatin plasma concentration versus time curve (AUC) = 6 × (glomerular filtration rate + 25) mg/m^2 (AUC6) plus paclitaxel 175 mg/m^2 for six cycles every 21 days or (2) carboplatin AUC6 plus paclitaxel 225 mg/m^2 for six cycles every 21 days. A total of 502 women entered the study.

Results
Pathologic complete response was documented in 132 patients (63.8%) in the 175 mg/m^2 group and in 127 cases (55.7%) in the 225 mg/m^2 group (χ^2 P = .090). The 4-year progression-free survival rate was 41.5% (SE = 3.5) in the 175-mg group and 39.2% (SE = 3.5) in the 225-mg group. The corresponding 4-year survival rates were 46.2% (based on 115 deaths) and 47.3% (based on 113 deaths), respectively.

Conclusion
This randomized trial suggests that paclitaxel 175 mg/m^2 plus carboplatin AUC6 is the schedule with a more favorable profile than paclitaxel 225 mg/m^2 plus carboplatin AUC6.

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INTRODUCTION

Cisplatinum plus paclitaxel is considered an optimal chemotherapy for treatment of advanced ovarian cancer [1-3]. Recently the combination of carboplatin and paclitaxel has been shown to have equal efficacy with less toxicity [4-6]. Common doses are paclitaxel 175 mg/m^2 and target area under the free carboplatin plasma concentration versus time curve (AUC) of 5 to 6 [6].

Data are scanty on the role of escalating doses of paclitaxel in combination with carboplatin at fixed doses [7-10]. Ten Bokkel Huinink et al [7] performed a pilot study with 46 patients to evaluate the combination with two doses of paclitaxel (125 and 200 mg/m^2) and carboplatin (300 and 600 mg/m^2); the overall response rate was 61% and was higher with the larger dose of paclitaxel.

Bolis et al [8] reported preliminary results of a phase I trial using a dose escalation of paclitaxel (150 to 250 mg/m^2) with a fixed dose of carboplatin (300 mg/m^2). The overall response rate was 86% in patients treated with ≤ 200 mg/m^2 of paclitaxel and 74% in those treated with ≥ 225 mg/m^2.

To analyze the effect of different doses of paclitaxel combined with fixed doses of carboplatin in the treatment of ovarian cancer, we conducted a large, randomized, clinical trial [11]. In this trial, carboplatin was

given before paclitaxel following our previous experience showing no sequence-dependent effect on toxicity [8].

PATIENTS AND METHODS

Entry criteria for this randomized, multicenter study were as follows: histologically confirmed epithelial ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] stages IIB to IV); Eastern Cooperative Oncology Group performance status ≤ 2; age less than 80 years; no history of other malignant diseases; no previous chemotherapy or radiotherapy; adequate hematologic, renal, hepatic, and cardiac functions as defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10$/L, platelet count $\geq 100 \times 10$/L, total bilirubin ≤ 1.25 times the upper normal limit, creatinine ≤ 1.5 times the upper normal limit, and no noteworthy ECG abnormalities. Brenner tumors and borderline, low-potential (grade 0) tumors were not included.

Within 28 days of cytoreductive surgery, eligible women were randomly assigned to treatment with (1) carboplatin at the dose (in milligrams) corresponding to the following formula: target AUC = 6 × [glomerular filtration rate + 25] mg/m^2 (AUC6) plus paclitaxel 175 mg/m^2 for six cycles every 21 days or (2) carboplatin AUC6 plus paclitaxel 225 mg/m^2 for six cycles every 21 days.

Randomization by phone was centralized. Separate randomization lists were used for each participating center and residual tumor after first-line surgery.

The glomerular filtration rate was calculated by the Cockcroft formula [12]. The dose corresponding to the AUC6 of carboplatin was administered in 30 minutes, without premedication diluted in 250 mL of D5W or normal saline.

All patients were then premedicated to prevent allergic reactions with chlorpheniramine 10 mg administered intramuscularly 1 hour before paclitaxel, hydrocortisone 500 mg administered intravenously 30 minutes before paclitaxel, and cimetidine 300 mg administered intravenously 30 minutes before paclitaxel, which was diluted in 1,000 mL of D5W. Only glass or polyolefin containers and polyethylene-lined nitroglycerin tubing are recommended for drug administration. Polyvinylchloride infusion sets were not used. Infusion time was 180 minutes for paclitaxel and 30 minutes for carboplatin.

Weekly counts were made in both treatment arms during each cycle of therapy to determine nadir counts and duration of toxicity. Other toxicities were recorded according to WHO recommendations [13].

Dose Reduction

Carboplatin was reduced for hematologic toxicity, and paclitaxel was reduced for hematologic and nonhematologic toxicity. The paclitaxel dose was reduced when neutropenia or thrombocytopenia (see Evaluation of Response) were present for 7 days or more (ie, two consecutive counts 1 week apart) or in case of febrile neutropenia with or without documented infection. The dose was reduced to 150 or 200 mg/m^2, respectively, if the ANC was between 1,000 and 1,500 $\times 10^9$/L and the platelet count was between 50 and 100 $\times 10^9$/L at nadir, and to 135 and 175 mg/m^2 if the ANC was between 500 and 1,000 $\times 10^9$/L or if the platelet count was less than 50 $\times 10^9$/L. In the same cases, the carboplatin dose was also reduced to AUC5 or AUC4, as clinically indicated. Treatment was delayed for a maximum of 2 weeks if the ANC was less than 1,500 $\times 10^9$/L or platelet count was less than 100 $\times 10^9$/L at the scheduled time of the next cycle.

In case of grade 3 gastrointestinal toxicity according the WHO classification or grade 1 to 2 neurologic toxicity, the dose of paclitaxel was reduced by 25 or 50 mg/m^2 as clinically indicated. In case of grade 3 to 4 neurologic or cardiac toxicity, treatment was stopped.

Evaluation of Response

After three cycles of treatment, patients were examined clinically, CA-125 was assayed, and the disease was reassessed by ultrasonography or computed tomography, as appropriate. An increase in CA-125 with no evidence of progression of the disease was not considered evidence of progression. If progression was observed, the patient was withdrawn from the study.

At the end of treatment, response was assessed as follows: clinical complete response (CR) was defined as complete disappearance of all clinically detectable tumor and negative CA-125 for at least two assays not less than 4 weeks apart. Pathologic CR was defined as disappearance of the disease at histologic examination assessed by at least eight random biopsies, with negative peritoneal cytology during second-look laparotomy or laparoscopy. Second-look surgery was not mandatory. Patients with no clinically or instrumentally measurable disease at randomization and those who did not undergo second-look surgery were included in the analysis for survival but not in the evaluation of response.

No specific instructions were given for management of patients after the study treatment or in case of discontinuation. However, the general policy of participating centers included second-line chemotherapy with a platinum-based compound in case of late recurrence or progression of disease (ie, >12 months after first-line treatment) and a scheme including anthracyclines in case of early recurrence/progression.

Before randomization, we recorded each patient's name, age, performance status, and FIGO stage. Other data were collected prospectively during the trial. Progression-free and survival status for each patient was reported to the coordinating center yearly. The research protocol was approved independently by the ethics committees of the individual centers, which established the procedures for obtaining informed consent.

A total of 502 women were randomly assigned. Of these, eight patients were not eligible (four because of age, two because of Eastern Cooperative Oncology Group performance status of 3, and two because of unknown FIGO stage) and were excluded from the analysis. Thus the present study is based on 244 women in the paclitaxel 175-mg/m^2 arm and 250 women in the 225-mg/m^2 arm. The patients were recruited in 11 centers (mean number of patients randomized per center, 45 patients; range, seven to 145 patients) from June 1993 to July 2000, with an average monthly randomization rate of 5.7 (range, 1 to 20).

Respectively, three (1.3%) and seven (2.8%) women in the 175-mg/m^2 and 225-mg/m^2 groups were lost to follow-up. They were considered in the analysis for the period during which they were in the trial.

Statistical Analysis

Survival was the end point for the main analysis of treatment effect, and survival was calculated from date of randomization to date of death (of any cause) or censored to the last follow-up date if no death occurred. Follow-up was updated in November 2000 for the majority of patients. Progression-free survival was calculated from the date of randomization to the date of clinical or pathologic progression or death, whichever came first.

Analysis was based on the intention-to-treat principle; in other words, patients remained in the allocated group regardless of whether the treatment assigned was given. Survival probabilities were estimated according to the Kaplan-Meier method and compared by the log-rank test [14,15].

The Cox model was fitted to the data after graphically checking the proportional hazards assumption to adjust the estimate of treatment effect and to assess the prognostic value of residual tumor size after first surgery, FIGO grade, stage, and histotype [16]. The Pearson χ^2 test for association was applied to test the relationship between treatment and response and to compare the impact of different types of toxicity in the two arms, when applicable.

Considering a 30% 4-year baseline survival, this study had 80% power to show a 10% absolute difference between the two arms, with a two-tailed log-rank test and alpha = 0.05 [17].

RESULTS

Table 1 shows the distribution of patients according to baseline characteristics. The two groups were similar in terms of baseline characteristics. For example, the median age was the same in both groups, and the proportion of stage IIIc was 71.2% in the 175-mg/m^2 paclitaxel group and 72% in the 225-mg/m^2 group. Likewise, the two groups had similar proportions of serous or mucinous histotype (67.2% and 64.7%), grade 1 to 2 cases (20.0% and 18.6%), residual tumor after first surgery greater than 1 cm (52.9% and 53.2%), and positive lymph nodes (53.1% and 54.1%).

Second-look surgery was performed in 79 cases in the 175-mg/m^2 group and in 67 cases in the 225-mg/m^2 group. No difference emerged in response to treatment (Table 2). CR was documented in 132 patients (pathologic in 70 patients) in the 175-mg/m^2 group and 127 patients (pathologic in 61 patients) in the 225-mg/m^2 group. Progression was observed in similar proportions in the two dosage arms.

Analysis in strata of residual disease showed no difference in the response for women with residual tumor ≤ 1 cm, greater than 1 cm, or carcinosis.

The median follow-up was 54 months in the 175-mg/m^2 group and 47 in the 225-mg/m^2 group. The 4-year progression-free survival rates were 41.5% (SE = 3.5) and 39.2% (SE = 3.5), respectively (log-rank test $\chi^2 = 0.033$; $P = .856$). The corresponding 4-year survival figures were 46.2% (based on 115 deaths) and 47.3% (based on 113 deaths; log-rank test $\chi^2 = 0.125$; $P = .724$; Fig 1). The 4-year survival rates were also largely similar in cases with residual tumor ≤ 1 cm (70.5% and 65.0%) or greater than 1 cm or carcinosis (33.0% and 37.1%).

The Cox model analysis (including terms for age, residual tumor, stage, histotype, and lymph node involvement) largely confirmed these findings, with the odds ratio of 4-year survival being 0.9 (95% CI, 0.7 to 1.3) for women given 225 mg/m^2 compared with women given 175 mg/m^2 of paclitaxel.

Table 1. Baseline Characteristics of Study Patients

	Paclitaxel Dose			
	175 mg/m^2		225 mg/m^2	
	No.	%	No.	%
Age, years				
Median	58		58	
Range	13-78		27-77	
Stage				
IIb	6	2.5	9	3.6
IIc	11	4.5	11	4.4
IIIa	6	2.5	3	1.2
IIIb	37	15.2	44	17.6
IIIc	175	71.2	180	72.0
IV	9	3.7	3	1.2
Histotype				
Serous	147	61.0	159	63.9
Mucinous	15	6.2	2	0.8
Endometrioid	32	13.3	27	10.8
Clear cell	40	16.6	51	20.5
Mixed	7	2.9	10	4.0
Grade				
1	9	3.8	6	2.4
2	39	16.2	40	16.2
3	188	78.3	198	80.2
4	4	1.7	3	1.2
Lymph nodes				
Positive	76	53.1	72	54.1
Negative	67	46.9	61	45.9
Residual tumor				
≤1 cm	88	36.4	90	36.3
>1 cm	128	52.9	132	53.2
Carcinosis	26	10.7	26	10.5

NOTE. In some cases, the sum does not add up to the total because of missing values.

Table 2. Response According to Treatment Group

	Paclitaxel Dose				
	175 mg/m^2		225 mg/m^2		
	No.	%	No.	%	P (χ^2)
Total series					.090
CR	132	63.8	127	55.7	
PR/NC	56	27.0	84	36.8	
PD	19	9.2	17	7.5	
Residual tumor ≤ 1 cm					.288
CR	63	78.8	57	67.9	
PR/NC	13	16.2	21	25.0	
PD	4	5.0	6	7.1	
Residual tumor > 1 cm					.106
CR	61	58.1	58	48.7	
PR/NC	31	29.5	51	42.9	
PD	13	12.4	10	8.4	
Carcinosis					.697
CR	8	36.4	11	45.8	
PR/NC	12	54.5	12	50.0	
PD	2	9.1	1	4.2	

NOTE. Data do not add up to the total because of missing values. Furthermore, in some patients, data were not available because of short follow-up.
Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

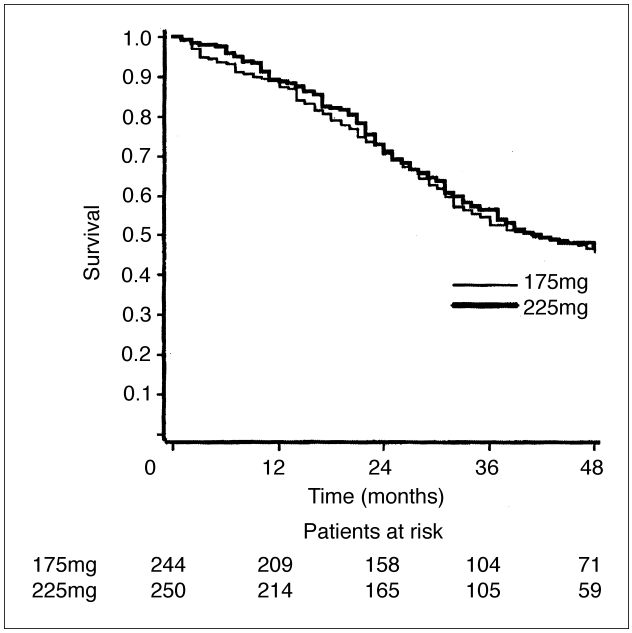

Fig 1. Survival according to study group.

The planned cycles were given to 207 of the women allocated to 175 mg/m^2 of paclitaxel and 219 of the women allocated to 225 mg/m^2. The dose of paclitaxel, carboplatin, or both was reduced in 59 women allocated to 175 mg/m^2 and in 91 women allocated to 225 mg/m^2. The scheduled doses without any delay were given to 170 patients in the 175-mg/m^2 group and to 162 patients in the 225-mg/m^2 group. Doses of carboplatin were reduced in 33 cases in the 175-mg/m^2 group and in 27 cases in the 225-mg/m^2 group. A delay in dose delivering was observed in 23 cases in the 175-mg/m^2 group and in 42 cases in the 225-mg/m^2 group.

We analyzed the 4-year survival in women who received the planned doses without any delay, and no difference emerged between the two groups ($P < .05$). Table 3 shows the reported toxicities: no real difference emerged in the frequency of toxicities in the two groups, except for alopecia, which was more frequent in the 175-mg/m^2 paclitaxel group, and neurotoxicity, which was more frequent in the 225-mg/m^2 paclitaxel group.

Thrombocytopenia grade 3 to 4 was reported in 40 cases in the 175-mg/m^2 group and in 49 cases in the 225-mg/m^2 group; this difference was not statistically significant. The mean cycle in which grade 3 to 4 thrombocytopenia was observed was similar in the two groups (5.6 cycle in the 175-mg/m^2 group and 5.8 in the 225-mg/m^2 group).

Table 3. Toxicity

	Paclitaxel Dose				
	175 mg/m^2		225 mg/m^2		
	No.	%	No.	%	$P(\chi^2)$
Allergic reaction					.754
Yes	11	4.8	10	4.2	
No	220	95.2	230	95.8	
Neutropenia grade					.243
0	42	18.0	37	15.3	
1	16	6.9	24	10.0	
2	40	17.2	27	11.2	
3	70	30.0	81	33.6	
4	65	27.9	72	29.9	
Thrombocytopenia grade					.391
0	96	41.2	112	46.7	
1	48	20.6	42	17.5	
2	49	21.0	37	15.4	
3	31	13.3	38	15.8	
4	9	3.9	11	4.6	
Anemia grade					.050
0	34	14.5	56	23.2	
1	82	35.0	68	28.2	
2	73	31.2	76	31.6	
3	43	18.4	35	14.5	
4	2	0.9	6	2.5	
Alopecia grade					.010
0	36	15.4	61	25.3	
1	1	0.4	1	0.4	
2	6	2.6	1	0.4	
3	188	80.3	178	73.9	
4	3	1.3	0	—	
Mucositis grade					.507
0	218	92.8	226	93.8	
1	17	7.2	14	5.8	
2	—	—	1	0.4	
Nausea and vomiting grade					.194
0	85	36.2	107	44.4	
1	98	41.7	87	36.1	
2	45	19.1	44	18.3	
3	7	3.0	3	1.2	
Myalgia grade					.743
0	140	59.6	143	59.3	
1	78	33.2	78	32.4	
2	15	6.4	15	6.2	
3	2	0.8	5	2.1	
Neurotoxicity grade					.001
0	81	34.5	63	26.0	
1	121	51.5	94	38.9	
2	31	13.2	70	28.9	
3	2	0.8	15	6.2	
Cardiotoxicity grade					.490
0	221	94.0	229	95.0	
1	14	6.0	11	4.6	
2	—	—	1	0.4	

NOTE. The sum does not add up to the total because of missing values.

DISCUSSION

This study found no substantial difference in response and survival between women treated with 175 mg/m^2 or 225 mg/m^2 of paclitaxel with carboplatin given to AUC6. However, neurotoxicity was more frequent in the higher dose group.

Published studies on the doses and dose-intensity of paclitaxel in the treatment of ovarian cancer are few and controversial. In a bifactorial design trial, 407 patients with

recurrent ovarian cancer were randomly assigned to one of two doses of paclitaxel (135 or 175 mg/m^2) and to one of two schedules (3 or 24 hours) after a standard regimen to prevent allergic reactions. Arthralgia/myalgia syndrome and peripheral neuropathy were more common in the higher dose arms. No significant difference emerged in clinical response [18].

In a small phase II trial of patients with relapsing ovarian cancer, the response rate seemed to increase with the dose, but the finding was based on a small number of patients [7]. The present study confirms the lack of difference in clinical response with low- or high-dose paclitaxel, in combination with carboplatin AUC6, in never-treated ovarian cancer.

In interpreting this finding, we have to take into account the limitations of the study. First, our study was powered to identify only a difference of 10% or more for 4-year survival. However, it is interesting to note the lower rate of response in women treated with the higher dose.

Another limitation is the fact that the overall differences in doses given to the two groups are not marked. We randomly assigned patients to receive 175 mg/m^2 of paclitaxel with carboplatin AUC6 or 225 mg/m^2 of paclitaxel, a dose less than 30% higher than the lower one. However, toxicity makes it impossible to give higher doses.

With regard to toxicity, the two schedules were generally safe. Toxicities grade 3 or 4, except for alopecia, were reported in approximately 35% in both groups. However, there was markedly more neurotoxicity in women treated with 225 mg/m^2 of paclitaxel. This is consistent with the Ten Bokkel Huinink findings and with a small phase II trial [8]. In the latter, there was no grade 2 to 3 neurotoxicity in 12 women treated with paclitaxel less than 200 mg/m^2 plus carboplatin 320 mg/m^2, but this incidence was 40% in 85 women treated with paclitaxel $\geq$ 225 mg/m^2 plus carboplatin 300 mg/m^2.

We found a higher frequency (statistically significant) of alopecia in patients treated with 175 mg/m^2 of paclitaxel. However, the difference in clinical terms was limited: in fact, only three cases with alopecia grade 4 were observed in the 175-mg/m^2 group.

In conclusion, this large, randomized trial suggests that paclitaxel 175 mg/m^2 plus carboplatin AUC6 is a more favorable schedule than paclitaxel 225 mg/m^2 plus carboplatin AUC6. Small differences in clinical response cannot be excluded on the basis of the present findings, but considering the higher frequency of neurotoxicity in the paclitaxel 225-mg/m^2 arm, the dose of 175 mg/m^2 should be considered the first choice. With an eye to the development of combination schedules, it is worth noting that paclitaxel does not seem to show dose-related efficacy.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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