Articles

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[A: abstract edited to conform with CONSORT guidelines (including deletion of secondary endpoints, inclusion of dropouts, and adverse events)]

Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase III, open-label, randomised controlled trial

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Summary

Background **Paclitaxel and carboplatin given every 3 weeks is standard treatment for advanced ovarian carcinoma. Attempts to improve patient survival by including other drugs have yielded disappointing results. We compared a conventional regimen of paclitaxel and carboplatin with a dose-dense weekly regimen in women with advanced ovarian cancer.**

Methods **Patients with stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were eligible for enrolment in this phase III, open-label, randomised controlled trial at 85 centres in Japan. Patients were randomly assigned by** xxxxxxxxxx [A: please provide method of randomisation] **to receive six cycles of either paclitaxel (180 mg/m²; 3-h intravenous infusion) plus carboplatin (area under the curve [AUC] 6 mg/mL per min), given on day 1 of a 21-day cycle (conventional regimen; n=320), or dose-dense paclitaxel (80 mg/m²; 1-h intravenous infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle (dose-dense regimen; n=317).** [A: please check added dose information] **The primary endpoint was progression-free survival. Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00226915.**

Findings **631 of the 637 enrolled patients were eligible for treatment and were included in the ITT population (dose-dense regimen, n=312; conventional regimen, n=319). Median progression-free survival was longer in the dose-dense treatment group (28·0 months** [A: please provide IQR or range]) **than in the conventional treatment group (17·2 months** [A: please provide IQR or range]; **hazard ratio [HR] 0·71; 95% CI 0·58–0·88; p=0·0015). Overall survival at 3 years was higher in the dose-dense regimen group (72·1%) than in the conventional treatment group (65·1%; HR 0·75, 0·57–0·98; p=0·03). 165 patients assigned to the dose-dense regimen and 117 assigned to the conventional regimen discontinued treatment early. Reasons for participant dropout were balanced between the groups, apart from withdrawal because of toxicity, which was higher in the dose-dense regimen group than in the conventional regimen group (n=113 *vs* n=69).** [A: new text ok?] **The most common adverse event was neutropenia (dose-dense regimen, 286 [92%] of 312; conventional regimen, 276 [88%] of 314) The frequency of grade 3 and 4 anaemia was higher in the dose-dense treatment group (214 [69%]) than in the conventional treatment group (137 [44%]; p<0·0001). The frequencies of other toxic effects were similar between groups.**

Interpretation Dose-dense weekly paclitaxel plus carboplatin improves survival compared with a conventional regimen of paclitaxel and carboplatin in women with advanced epithelial ovarian cancer. [A: rather than repeating the results here, please mention the implication of the findings for clinical practice]

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Introduction

Paclitaxel and carboplatin given every 3 weeks is currently considered standard first-line chemotherapy for advanced epithelial ovarian cancer. The consensus statements on the management of ovarian cancer at the 3rd International Gynecologic Cancer Consensus Conference in 2004 recommended intravenous paclitaxel (175 mg/m² over 3 h) plus intravenous carboplatin (area under the curve [AUC] 5·0–7·5 mg/mL per min) given every 3 weeks for six cycles for first-line chemotherapy.[1] Paclitaxel and carboplatin have been combined with other drugs, given either concurrently or sequentially, in the hope of prolonging survival in women with advanced ovarian cancer, but the results of several randomised trials have been disappointing.[2–4] In particular, the recently reported randomised trial of the Gynecologic Oncology Group, an international collaborative study enrolling more than 4500 patients, showed that the addition of new cytotoxic drugs to paclitaxel plus carboplatin did not improve progression-free or overall survival.[2]

Dose-dense weekly administration of paclitaxel is another strategy to enhance antitumour activity and prolong survival. Preclinical studies have suggested that duration of exposure is an important determinant of the cytotoxic activity of paclitaxel.[5] Adequate cytotoxicity can be achieved at fairly low concentrations of the drug provided that exposure is extended.[5,6] Several phase II clinical trials of dose-dense weekly paclitaxel and

carboplatin have shown promising efficacy and favourable tolerability in women with ovarian cancer.[7–9]

We undertook a phase III, randomised controlled trial to compare conventional paclitaxel and carboplatin given every 3 weeks with dose-dense paclitaxel given every week plus carboplatin (every 3 weeks) as first-line treatment in women with advanced ovarian cancer.

Methods

[A: text in this section has been moved and subheadings changed to conform with journal style]

Patients

Patients from 85 centres in Japan were eligible for enrolment in this phase III, open-label, randomised trial if they had a histologically or cytologically proven diagnosis of stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. If only the results of cytological examinations were available, patients needed to have the following criteria: (1) a cytological diagnosis of adenocarcinoma; (2) an abdominal mass more than 2 cm in diameter on abdominal images; and (3) a CA125/carcinoembryonic antigen (CEA) ratio[10] of more than 25, or no evidence of gastrointestinal cancer if CA125/CEA ratio was less than or equal to 25. Previous chemotherapy was not allowed. Patients needed to be aged 20 years or older, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 [A: please provide reference for this scale],[11] and to have adequate organ functions, defined as absolute neutrophil count 1·5 cells × 10^9 per L or more, platelet count 100 × 10^9 per L or more, serum bilirubin 25·7 μmol/L or less, serum aspartate aminotransferase 100 IU/L or less, and serum creatinine 132·6 μmol/L or less [A: all values converted into SI units. Please check all conversions have been done correctly]. Patients were excluded if they had an ovarian tumour with a low malignant potential, or synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ.

All patients gave [A: written?] informed consent before enrolment in this study. The study protocol was approved by the institutional review boards at all participating centres. The protocol was coordinated by the Japanese Gynecologic Oncology Group (protocol number 3016).

To view the full protocol of this trial see http:// [A: please provide URL where protocol can be accessed]

Randomisation and masking

Patients were randomly assigned to receive paclitaxel and carboplatin in either a conventional regimen (control) or a dose-dense regimen (intervention). Randomisation was by telephone or fax from a dedicated centre [A: ok?], and stratified by residual tumour diameter (≥1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics (FIGO) stage (II *vs* III *vs* IV) [A: please provide reference for this scale],[12] and histological type (clear-cell or mucinous tumours *vs* serous or other tumours), with an option to avoid the imbalance greater than 2 within each institution [A: I am not sure what you mean here, please rephrase to clarify]. Patients and clinicians were not masked to treatment assignment [A: ok?]. [A: please also add the following information to this section: *Sequence generation*. a description of the actual method of randomisation (ie, the method used to generate the sequence with which participants are allocated to comparison groups [eg, computer randomisation], including details of the methods used to restrict the randomisation—eg, block, stratification). *Implementation*. Who generated the allocation sequence, who enrolled participants, and who assigned them to the trial groups]

Procedures

Both study groups received carboplatin at a dose calculated to produce an AUC of 6 mg/mL per min on day 1 of a 21-day cycle. Carboplatin was given as an intravenous infusion over 1 h. The control group also received paclitaxel given as a 3-h intravenous infusion at a dose of 180 mg/m² on day 1. In the dose-dense group, paclitaxel was given as a 1-h intravenous infusion at a dose of 80 mg/m² on days 1, 8, and 15. The dose of carboplatin was calculated with the formula of Calvert and colleagues,[13] by use of creatinine clearance instead of glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[14] Standard premedication was given to prevent hypersensitivity reactions to paclitaxel. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy.

Patients needed to have an absolute neutrophil count of 1·0×10^9 cells per L [A: conversion ok?] (amended from 1·5×10^9 cells per L on April 11, 2005, because of frequent occurrence of delaying) or more and a platelet count of 75×10^9 per L or more to receive subsequent cycles of therapy in both groups. Patients in the dose-dense regimen group also had to have an absolute neutrophil count of 0·5×10^9 cells per L or more and a platelet count of 50×10^9 per L (amended from 7·5×10^9 per L on April 11, 2005) or more before they received paclitaxel on days 8 and 15. [A: all values in this paragraph converted to our preferred format (in L). Please check carefully] Treatment was delayed for a maximum of 3 weeks (amended from 2 weeks on April 11, 2005).

Carboplatin was reduced for haematological toxicity, and paclitaxel was reduced for non-haematological toxicity with dose reduction levels as follows: carboplatin AUC 5 mg/mL per min [A: units correct?] (level 1) or AUC 4 mg/mL per min [A: units correct?] (level 2) in both groups; paclitaxel 135 mg/m² (level 1) or 110 mg/m² (level 2) in the conventional treatment group, and paclitaxel 70 mg/m² (level 1) or 60 mg/m² (level 2) in the dose-dense treatment group. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count less than 0·5×10^9 cells per L persisted for 7 days or more, the platelet count was less than 10×10^9

per L, the platelet count was between 10×10^9 per L and 50×10^9 per L with bleeding tendencies, or the treatment was delayed for haematological toxicity for more than 1 week. [A: values in this paragraph converted to our preferred format. Please check carefully] In general, patients did not receive prophylactic granulocyte-colony stimulating factor (G-CSF) unless they had treatment delays or neutropenic complications after treatment. The dose of paclitaxel was reduced in patients who had grade 2 or higher peripheral neuropathy.

Interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both, were allowed. These procedures were done within 6 weeks after chemotherapy, and subsequent chemotherapy was restarted within 6 weeks after surgery.

The primary endpoint of this trial was progression-free survival, defined as the time from the date of randomisation to the date of the first occurrence of any of the following events: death from any cause; appearance of any new lesions that could be measured or assessed clinically; or CA125 criteria of disease progression.[15] The CA125 criteria of disease progression were defined as (1) patients with raised CA125 concentration before treatment, with a return to normal that showed evidence of CA125 greater than or equal to two times the upper normal limit [A: if returned to normal how can this occur?]; (2) patients with raised CA125 before treatment that did not return to normal needed to show evidence of CA125 greater than or equal to two times the nadir value; or (3) patients with CA125 in the normal range before treatment needed to show evidence of CA125 greater than or equal to two times the upper normal limit, with raised CA125 recorded on two occasions at least 1 week apart. In patients with measurable disease, clinical or radiographical tumour measurements had priority over CA125 concentration, and progression during treatment could not be declared on the basis of CA125 alone.

Secondary endpoints were overall survival, response rate, and adverse events. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat (ITT) principle. Clinical response was assessed in eligible patients with lesions that could be measured in two dimensions. The assessment of response had to be confirmed on two occasions at least 4 weeks apart. A complete response was defined as the complete disappearance of all measurable and assessable lesions, determined by two observations not less than 4 weeks apart. A partial reponse was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of measurable lesions, determined by two observations not less than 4 weeks apart. Stable disease was defined as a steady state of response less than a partial response or as an increase of less than 25% in the sum of the products of the perpendicular diameters of measurable lesions, lasting at least 4 weeks. Progressive disease was defined as an unequivocal increase of at least 25% in the sum of the products of the perpendicular diameters of measurable lesions. The appearance of new lesions also constituted progressive disease. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[16] [A: please provide reference][A: repetition of next section deleted from here]

Radiological studies to record the status of all measurable lesions noted at baseline were repeated after two, four, and six cycles of chemotherapy. Once patients discontinued the protocol therapy, disease status was assessed every 3 months for the first 2 years and every 6 months thereafter. Follow-up monitoring included clinical examinations and CA125 concentration estimation; routine CT scans were not required, but were requested if CA125 concentration rose, symptoms of

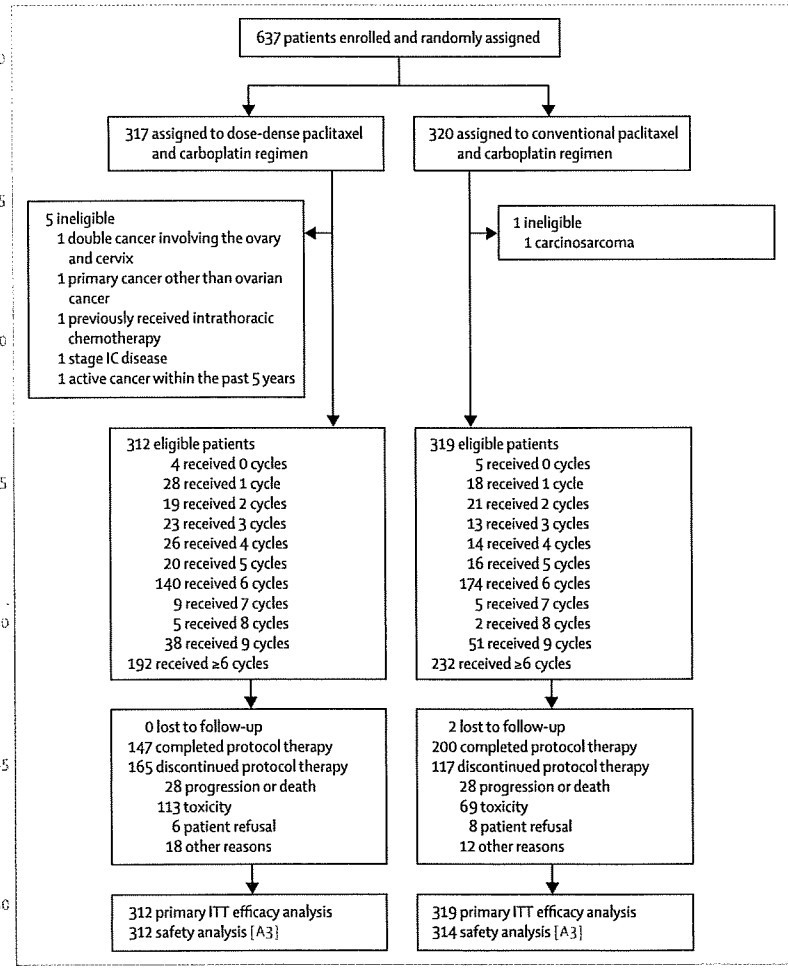

Figure 1: **Trial profile**

ITT=intention-to-treat. [A1: reasons for ineligibility have been added to the figure. Please check that the patients are listed in the correct trial groups] [A2: figure edited so that the intervention is on the left (to conform with house style)] [A3: if all randomised patients who received at least one cycle are analysed, why are there 314 in the conventional group (320 randomised minus 5 with no cycles=315) and 312, not 313 in the dose-dense group (317 minus 4 with no cycles=313)?]

	Dose-dense regimen group (n=312)	Conventional regimen group (n=319)
Median age (years)	57 (25–87)	57 (25–84)
FIGO stage		
II	62 (20%)	54 (17%)
III	202 (65%)	215 (67%)
IV	48 (15%)	50 (16%)
ECOG performance status		
0 or 1	283 (91%) [A1]	287 (90%)
2	23 (7%)	20 (6%)
3	6 (2%)	12 (4%)
Disease		
Ovarian	260 (83%)	276 (87%)
Fallopian tube	14 (4%) [A1]	18 (6%)
Primary peritoneal	38 (12%)	25 (8%)
Surgery		
Cytology only	35 (11%)	35 (11%)
Primary debulking	277 (89%)	284 (89%)
Interval debulking	34 (11%)	29 (9%)
Secondary/second-look	38 (12%)	56 (18%)
Residual disease		
≤1 cm	144 (46%)	145 (45%)
>1 cm	168 (54%)	174 (55%)
Histological type		
Serous adenocarcinoma	173 (55%)	182 (57%)
Endometrioid adenocarcinoma	38 (12%)	39 (12%)
Clear-cell carcinoma	31 (10%)	37 (12%)
Mucinous adenocarcinoma	23 (7%)	11 (3%)
Other types	47 (15%)	50 (16%)
Histological grade		
Well differentiated	42 (13%) [A2]	40 (13%) [A2]
Moderately differentiated	60 (19%)	71 (22%)
Poorly differentiated	79 (25%)	72 (23%)
Unknown/not applicable	131 (42%)	136 (43%)

Data are n (%) or median (range). FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. [A: in the submitted table, there was an asterisk next to FIGO—should there be a footnote relating to this?] [A1: percentage corrected, ok?] [A2: these %s have been corrected—they were very wrong in the original (32% and 31%) - please check]

Table 1: **Baseline characteristics of study patients**

relapse developed, or both. [A: what was the final follow-up time?]

Statistical analysis

Our hypothesis was that the dose-dense regimen would prolong progression-free survival compared with the conventional regimen. At the beginning of the study in April, 2003, a sample size of 380 patients with no interim analysis was initially planned to detect a 37·5% improvement in median progression-free survival in the conventional regimen group (from 16 months to 22 months) with 80% power, two-sided log-rank test, and alpha level of 0·05. In January, 2005, the sample size was increased to 600 patients during the trial to account for the higher accrual of patients and to detect a shorter prolongation of progression-free survival. This amendment of the protocol was made without interim analysis and was approved by the data and safety monitoring committee. The increased sample size would enable the detection of a 31·3% improvement (from 16 months to 21 months) in median progression-free survival with 80% power, two-sided log-rank test, at an alpha level of 0·05, an accrual of 3 years, and a follow-up of 1·5 years. Following the data safety monitoring committee's instructions, interim analysis was planned after 380 patients had been randomly assigned to treatment, and multiplicity by multiple look was adjusted with the O'Brien-Fleming alpha-spending function. At the first interim analysis in December, 2005, the data safety monitoring committee reviewed the results and approved continuation of the planned follow-up.

The cumulative survival curve and median progression-free survival time were estimated by use of the Kaplan-Meier method [A: addition ok?]. Adverse events were analysed in all randomised women who had received at least one cycle of treatment. A: if all randomised patients who received at least one cycle are analysed, why are there 314 in the conventional group (320 randomised minus 5 with no cycles=315) and 312, not 313 in the dose-dense group (317 minus 4 with no cycles=313)?] Proportions of adverse events were compared between the groups by the use of two-sided χ^2 tests or two-sided Fisher's exact tests. Responses were compared by the use of Fisher's exact test. All analyses were performed with SAS software, version 8.2. This trial is registered with ClinicalTrials.gov, number NCT00226915.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

[A: subheadings removed to conform with house style. Also, to avoid repetition, any data that are clearly shown in the figures and tables have been deleted from the text] Between April, 2003, and December, 2005, 637 patients were enrolled at 85 centres. [A: I count 86 centres listed at the end of the paper—why is this?] Figure 1 shows the trial profile. [A: reasons for ineligibility have been added to figure 1. Please check the reasons are under the correct group] Table 1 shows the baseline characteristics of the 631 eligible patients whose data were included in the ITT analysis. [A: unnecessary text deleted since any differences between groups at this point would be a result of chance]

[A: please check the percentages given in table 1, as under "histological grade, well differentiated", it appears

that 40 patients (conventional group) and 42 patients (dose-dense group) should both be 13% of the total numbers of patients]

The median number of treatment cycles was six in both groups (figure 1). The proportion of patients who received six or more cycles of treatment was higher in the conventional regimen group (232 [73%] of 319) than in the dose-dense regimen group (192 [62%] of 312). The main reason for discontinuing treatment was toxicity. Haematological toxicity was the most common form of toxicity leading to the discontinuation of treatment (68 [60%] of 113 patients assigned to the dose-dense regimen *vs* 30 [43%] of 69 assigned to the conventional regimen; p=0·03). The proportions of patients who discontinued treatment because of neurotoxicity were low in both groups (three [3%] *vs* five [7%]). Other reasons for discontinuation of treatment because of toxicities were patient refusal (13 [12%] *vs* 12 [17%]), allergic reaction (four [4%] *vs* seven [10%]), and other toxicities (25 [22%] *vs* 15 [22%]). At least one treatment cycle was delayed in a higher proportion of patients in the dose-dense treatment group (236 [76%] of 312) than in the conventional treatment group (213 [67%] of 319; p=0·02). The dose of the study drugs was reduced in a higher proportion of patients assigned to the dose-dense regimen (150 [48%] of 312) than in those assigned to the conventional regimen (112 [35%] of 319; p=0·001). The mean delivered dose intensity of carboplatin was lower in the dose-dense regimen group (AUC per week 1·54 mg/mL per min [SD xx] [A: units correct? Please provide SD to accompany mean]) than in the conventional regimen group (1·71 mg/mL per min [SD xx] [A: units correct? Please provide SD to accompany mean]), and the mean delivered dose-intensity of paclitaxel was higher (63·0 mg/m² per week [SD xx] *vs* 51·7 mg/m² per week [SD xx] [A: please provide SDs]). The mean relative dose-intensities of carboplatin and paclitaxel were both lower in the dose-dense regimen group (0·77 [A: units? SD?] and 0·79 [A: units? SD?], respectively) than in the conventional regimen group (0·85 [A: units? SD?], and 0·86 [A: units? SD?], respectively).

At the time of last follow-up [A: when was this?], there had been 160 disease progression events in the dose-dense treatment group and 200 in the conventional treatment group [A: are these numbers correct?]. After a median duration of follow-up of 29 months, median progression-free survival was 28·0 months ([A: please provide IQR or range]) in the dose-dense treatment group and 17·2 months ([A: please provide IQR or range]) in the conventional treatment group (figure 2; unadjusted hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0015, log-rank test). When the analysis was done with data from all 637 patients who were randomly assigned to treatment, the result was similar (p=0·0019). After adjustment for FIGO stage, residual disease, and histological type according to the preplanned analysis, the HR was 0·65 (0·53–0·80; p=0·0001). We subsequently undertook unplanned sensitivity analyses. The differences between groups were still significant when only clinical progression was defined as progression (p=0·0018), when data on patients who received second-line therapy before progression were censored (eight patients [A: from which groups?]; p=0·0018), or when data on patients who underwent interval or secondary surgery were censored (157 patients [A: correct number?]; p=0·0092).

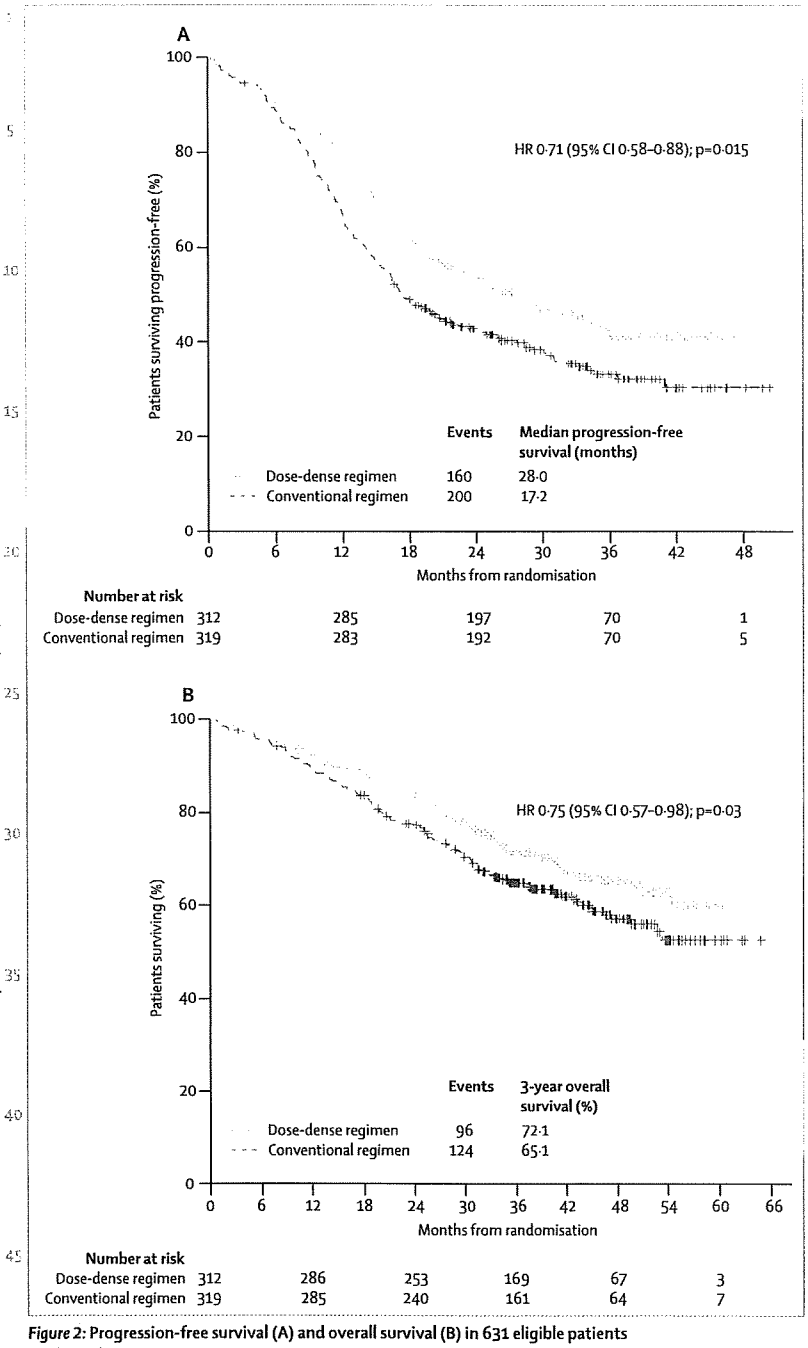

Figure 2: **Progression-free survival (A) and overall survival (B) in 631 eligible patients**
HR=hazard ratio.

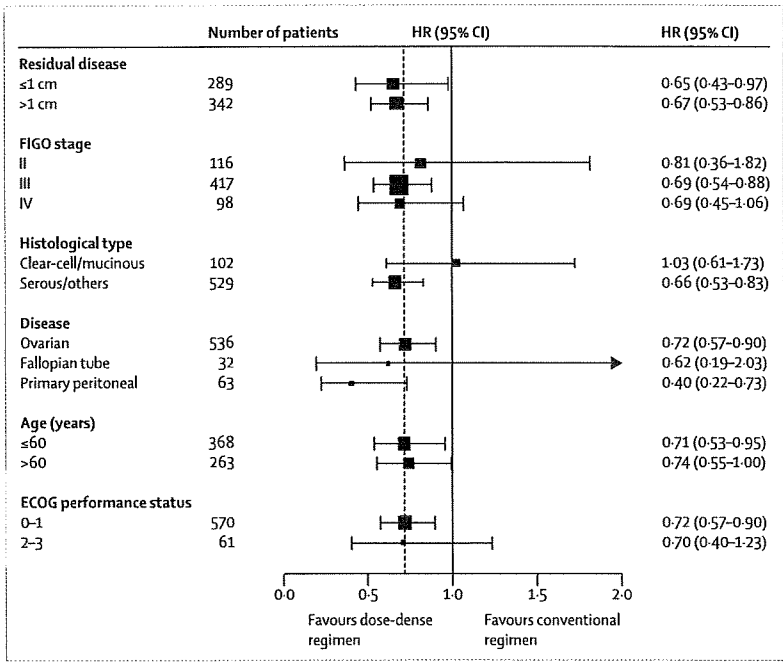

Figure 3: **Progression-free survival according to baseline characteristics**
FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. The hazard ratios (HRs; 95% CIs) are for patients assigned to conventional paclitaxel and carboplatin, compared with those assigned to dose-dense paclitaxel and carboplatin, and were obtained from the unadjusted Cox model. The dashed vertical line indicates a hazard ratio of 0·71, which is the value for all patients, and the solid vertical line indicates a hazard ratio of 1·00, which is the null-hypothesis value.

Analysis of overall survival was done in December, 2007, at the same time as the analysis of progression-free survival. The overall survival at 2 years was 83·6% in the dose-dense treatment group and 77·7% in the conventional treatment group (p=0·049). We updated the overall survival analysis in December, 2008, with median follow-up period of 42 months. Although median overall survival had not been reached in either group, overall survival at 3 years was higher in the dose-dense treatment group (72·1%) than in the conventional treatment group (65·1%; unadjusted HR 0·75, 0·57–0·98; p=0·03 log-rank test).

A Cox proportional-hazards model was used to examine the effect of baseline clinical characteristics and conventional prognostic factors on the treatment effect (figure 3). Progression-free survival was longer in the dose-dense treatment group than in the conventional treatment group across all subgroups of patients apart from in those with clear-cell or mucinous tumours. In this subgroup of patients, the HR in the dose-dense treatment group was similar to that in the conventional treatment group.

Clinical response was assessed in 282 patients who had measurable disease at study entry. The overall response rate was similar between groups (conventional regimen, 72 [53%] patients; dose-dense regimen, 82 [56%] patients; p=0·72; table 2). Because patients with suboptimal [A: meaning?] disease were allowed to undergo interval debulking surgery in this study, response sometimes could not be confirmed on repeated imaging. If these unconfirmed responses are taken into account [A: how many?], the overall response rate was 70% (n=xx? [A: actual number?]) in the conventional treatment group compared with 71% (n=xx? [A: actual number?]) in the dose-dense treatment group (p=0·90).

Treatment-related adverse events were analysed in patients who received at least one cycle of the study treatment (table 3). The frequency of grade 3 or 4 anaemia was higher in the dose-dense treatment group than in the conventional treatment group (p<0·0001). Recombinant erythropoietin was not used to treat anaemia [A: ok?] because it was not approved in Japan. G-CSF was used in xx [A: actual numbers please] (38%) patients assigned to the dose-dense regimen and in xx (47%) assigned to the conventional regimen. The frequency of neuropathy did not differ between study groups.

Discussion

Our study showed that compared with a conventional regimen, dose-dense treatment with paclitaxel and carboplatin improved progression-free survival in women with newly diagnosed, stage II to IV ovarian cancer. Women assigned to dose-dense paclitaxel and carboplatin had a 29% lower risk of disease progression and a 25% lower risk of death than did patients assigned to the conventional regimen. Benefits of this magnitude have been rare in women with advanced ovarian cancer, including those with suboptimally debulked stage III and IV disease, since the approval of paclitaxel for the indication of ovarian cancer.

The concept of dose density is based on the hypothesis that a shorter interval between doses of cytotoxic therapy would more effectively reduce tumour burden than would dose escalation.[17] In breast cancer, recently published phase III trials have shown that paclitaxel given every a week improves response and survival.[18,19] Consistent with these findings, our study showed that progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group. Increased doses of paclitaxel of 225 mg/m² or 250 mg/m² given every 3 weeks have been compared with the standard dose (ie, 175 mg/m²) in women with ovarian cancer, but showed no benefit in survival.[20,21] Our study showed a survival advantage with an increased total dose of 240 mg/m², given in three divided doses during a 21-day cycle, suggesting that dose density is more important than increased dose intensity.

There was greater haematological toxicity in the dose-dense treatment group than in the conventional treatment group, which resulted in more delays and dose modifications. The optimum dose and schedule of dose-dense paclitaxel and carboplatin have not yet been established. Rose and colleagues[8] reported that weekly

	Dose-dense regimen group (n=147)	Conventional regimen group (n=135)	p value
Complete response	29 (20%)	21 (16%)	x·xx
Partial response	53 (36%)	51 (38%)	x·xx
Stable disease	43 (29%)	42 (31%)	x·xx
Progressive disease	4 (3%)	9 (7%)	x·xx
Not evaluable	18 (12%)	12 (9%)	x·xx

See Methods section for definitions of responses. [A: please provide p values for data]

Table 2: **Clinical response in patients with measurable lesions**

	Dose-dense regimen group (n=312)	Conventional regimen group (n=314)	p value
Neutropenia	286 (92%)	276 (88%)	0·15
Thrombocytopenia	136 (44%)	120 (38%)	0·19
Anaemia	214 (69%)	137 (44%)	<0·0001
Febrile neutropenia	29 (9%)	29 (9%)	1·00
Nausea	32 (10%)	36 (11%)	0·70
Vomiting	9 (3%)	11 (4%)	0·82
Diarrhoea	10 (3%)	8 (3%)	0·64
Fatigue	15 (5%)	8 (3%)	0·14
Arthralgia	3 (1%)	5 (2%)	0·72
Myalgia	2 (1%)	4 (1%)	0·69
Neuropathy (motor)	15 (5%)	12 (4%)	0·56
Neuropathy (sensory)	21 (7%)	20 (6%)	0·87

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.16

Table 3: **Frequency of grade 3 or 4 adverse events**

paclitaxel at a dose of 60 mg/m² in combination with carboplatin at an AUC of 5 [A: units?] was tolerated and active in patients with recurrent ovarian cancer. An alternative schedule of dose-dense treatment is to give both paclitaxel and carboplatin every week. Sehouli and co-workers[9] showed that weekly paclitaxel at a dose of 100 mg/m² and weekly carboplatin at an AUC of 2 [A: units?] showed substantial activity and tolerability in patients with primary ovarian cancer. A treatment delay occurred in only 2·8% of patients [A: ok?] and the frequency of grade 3 neurotoxicity (x%) [A: please provide % from reference 9] was lower than that reported in our study. Additionally, weekly carboplatin of AUC 2 [A: units?] and weekly paclitaxel of 60 mg/m² on days 1, 8, and 15 every 4 weeks showed a favourable toxicity profile in elderly ovarian cancer patients.[22]

The response rate did not differ between groups. Virtually all previous randomised trials in ovarian cancer that showed an improvement in progression-free survival and overall survival also had a higher response rate for the more effective treatment. A lower dose of paclitaxel had antiangiogenic activity in a xenograft model.[23] Antiangiogenic agents might promote tumour dormancy by maintaining tumour size and preventing outgrowth.[24] Vascular endothelial growth factor (VEGF) is frequently expressed in ovarian cancer, and might be an important therapeutic target. Longer survival in the dose-dense regimen group without an improved response rate might be attributed to the antiangiogenic effect of paclitaxel. Anti-VEGF agents such as bevacizumab combined with the dose-dense treatment will be assessed in future trials.

Neurotoxicity is the adverse reaction of greatest concern in patients who receive a combination of paclitaxel and carboplatin. In breast cancer trials, the incidence of neurotoxicity was higher in patients given paclitaxel every week than in patients given paclitaxel every 3 weeks.[19] In our study, however, the frequency of neurotoxicity was similar in both groups. This finding might be because patients in the dose-dense treatment group discontinued treatment more often than did those in the dose-dense treatment group.

Fewer than half the patients assigned to the dose-dense regimen completed treatment according to the study protocol. When designing the protocol, we debated whether patients who responded to six cycles of chemotherapy should receive three more cycles. However, this study was not designed to assess the relation between the duration of treatment and clinical outcomes, and there is little evidence to suggest that more than six cycles of chemotherapy would prolong survival. About 60% of patients in the dose-dense regimen group received six or more cycles of chemotherapy. Treatment cycles were more frequently delayed in the dose-dense treatment group than in the conventional treatment group, mainly because of neutropenia. [A: apart from treatment compliance, what are the other limitations of the study? (eg, open-label trial, so would ideally be confirmed in a masked trial, and maybe in a different ethic group?)]

Clear-cell and mucinous adenocarcinoma of the ovary is associated with low sensitivity to chemotherapy and poor survival.[25,26] In our study, neither dose-dense nor conventional treatment seemed effective against clear-cell or mucinous ovarian carcinoma, which suggests that other treatment strategies are needed.

Thus, our study showed that a dose-dense regimen of paclitaxel once a week plus carboplatin every 3 weeks is associated with longer progression-free and overall survival than a conventional regimen of paclitaxel and carboplatin given every 3 weeks in women with advanced epithelial ovarian cancer.

Contributors

NK, MY, FT, SI, TS, EK, and KO conceived and designed the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator for the study. NK and FT analysed and interpreted the results. NK drafted the report. KN was responsible for the overall planning and conduct of the study. NK, MY, SI, TJ, DA, HT, TS, SK, EK, and KO were involved in the provision of study material or patients, or data acquisition. NK, MY, TS, EK, and KO were members of the steering committee. All authors were involved in writing the report and approved the final version of the manuscript.

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Conflicts of interest

SI and DA have received honoraria from Bristol-Myers Squibb. DA and HT have received grant support from Bristol-Myers Squibb. All other authors declare that they have no conflicts of interest. [A: is this correct?]

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文献 3

The New England Journal of Medicine

INTRAPERITONEAL CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE VERSUS INTRAVENOUS CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE FOR STAGE III OVARIAN CANCER

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ABSTRACT

Background Intravenous platinum-based chemotherapy is the standard primary therapy for advanced ovarian cancer. We conducted a phase 3 trial to compare the effects of intraperitoneal and intravenous cisplatin on the survival of women with previously untreated, stage III, epithelial ovarian cancer.

Methods The patients underwent an initial exploratory laparotomy and resection of all tumor masses larger than 2 cm. Within four weeks after surgery, six courses of intravenous cyclophosphamide (600 mg per square meter of body-surface area per course) plus either intraperitoneal cisplatin (100 mg per square meter) or intravenous cisplatin (100 mg per square meter) were administered at three-week intervals.

Results Of 654 randomized patients, 546 were eligible for the study. The estimated median survival was significantly longer in the group receiving intraperitoneal cisplatin (49 months; 95 percent confidence interval, 42 to 56) than in the group receiving intravenous cisplatin (41 months; 95 percent confidence interval, 34 to 47). The risk of death was lower in the intraperitoneal group than in the intravenous group (hazard ratio, 0.76; 95 percent confidence interval, 0.61 to 0.96; P=0.02). Moderate-to-severe tinnitus, clinical hearing loss, and neuromuscular toxic effects were significantly more frequent in the intravenous group.

Conclusions As compared with intravenous cisplatin, intraperitoneal cisplatin significantly improves survival and has significantly fewer toxic effects in patients with stage III ovarian cancer and residual tumor masses of 2 cm or less. (N Engl J Med 1996;335: 1950-5.)

OVARIAN cancer, the leading cause of death from gynecologic cancer in the United States, is one of the few solid tumors in which the five-year survival rate for patients has improved in recent years.[1,2] Nevertheless, most women with advanced ovarian cancer die of the disease. Even those with stage III cancer and minimal residual intraperitoneal masses (≤2 cm in the greatest dimension) have a median survival of only about 40 months.[3,4]

Standard chemotherapy for advanced ovarian cancer includes a platinum analogue (either cisplatin or carboplatin). In an attempt to maximize its activity against ovarian cancer, cisplatin has been administered directly into the peritoneal cavity in investigational studies.[5] This route yields an intraperitoneal concentration of cisplatin that is 12 to 15 times greater than the plasma concentration.[6,7] Some phase 2 studies have suggested that survival is prolonged in patients with small residual masses (<1 cm) who receive salvage intraperitoneal chemotherapy after initial chemotherapy and second-look surgery.[8,9] The present phase 3 trial compares cisplatin administered intraperitoneally with cisplatin administered intravenously in patients with previously untreated stage III ovarian cancer and residual masses no larger than 2 cm in the greatest dimension.

METHODS

Patients

Within four weeks before enrollment, patients underwent an initial exploratory laparotomy with at least bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy, and debulking of all tumor nodules to a size of 2 cm or less in the greatest dimension. The Southwest Oncology Group's Gynecologic Surgical Review Board reviewed the surgical results to confirm eligibility for enrollment. Only patients with a histologic diagnosis of epithelial-type ovarian cancer were eligible.

Eligible patients had stage III disease, a performance status of 0 to 2 (according to criteria established by the Southwest Oncology Group), normal blood counts, and adequate renal function (serum creatinine, ≤1.5 mg per deciliter [130 μmol per liter]; creatinine clearance, ≥40 ml per minute). All patients gave informed consent according to institutional and federal guidelines before enrollment.

Treatment Plan

Patients were randomly assigned to receive intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin plus intravenous cyclophosphamide. The randomization procedure incorporated stratification according to the amount of residual tumor (≤0.5 cm vs. >0.5 cm to 2 cm), performance status (0 or 1 vs. 2), the timing of enrollment (during vs. after surgery),

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and the cooperative group (Southwest Oncology Group vs. Gynecologic Oncology Group vs. Eastern Cooperative Oncology Group).

Patients in both treatment groups received cyclophosphamide (600 mg per square meter of body-surface area in 150 ml of diluent) administered in a 60-to-90-minute intravenous infusion on day 1. Patients in the intravenous group received cisplatin (100 mg per square meter in 500 to 1000 ml of normal saline) administered intravenously at a rate of 1 mg per minute, followed by at least 1 liter of normal saline with 3 g of magnesium sulfate and 40 g of mannitol over a period of one to two hours on day 1. Patients in the intraperitoneal group received cisplatin (100 mg per square meter in 2 liters of normal saline) warmed to body temperature and instilled into the peritoneal cavity as rapidly as possible. Concurrently, these patients received at least 1 liter of normal saline with 3 g of magnesium sulfate and 40 g of mannitol intravenously.

Courses of cyclophosphamide and cisplatin were repeated every three weeks for a total of six cycles, provided the serum creatinine concentration was less than or equal to 1.9 mg per deciliter (170 μmol per liter), the white-cell count was higher than 3000 per cubic millimeter, and the platelet count was higher than 100,000 per cubic millimeter. Therapy could be delayed for a maximum of two weeks to allow for the resolution of toxic effects. Cisplatin was permanently discontinued and the dose of cyclophosphamide increased to 1 g per square meter (in the absence of grade 3 or 4 myelosuppression) if peripheral neuropathy of grade 2 or higher developed or the serum creatinine concentration rose above 1.9 mg per deciliter. Therapy was discontinued altogether if the serum creatinine level remained higher than 1.9 mg per deciliter for eight weeks.

Clinical and Pathological Assessments

At base line and after six courses of therapy, a physical examination was performed, with a complete blood count, serum CA-125 and blood chemical measurements, and chest radiography. In addition, before each cycle, a physical examination was performed, with a complete blood count and measurement of serum CA-125 and creatinine concentrations. Blood chemical measurements were performed at the start of every other course. At the completion of therapy, patients without clinical evidence of ovarian cancer (excluding an elevated serum CA-125 value) underwent a second-look laparotomy to determine whether there had been a pathological response.

A complete pathological response was defined as no pathological evidence of disease on second-look surgery and biopsy of the upper abdomen and the para-aortic and retroperitoneal lymph nodes, as well as any other site previously involved with tumor.

Statistical Analysis

In the original study design (before the protocol was amended to increase enrollment), it was assumed that 215 eligible patients would be randomly assigned to each treatment group. At a two-sided P value of 0.05, with the use of a Pearson chi-square approximation, the estimated power was 0.85 to detect a difference of 55 percent versus 40 percent in pathological-response rates in the intraperitoneal and intravenous groups, respectively. The power was 0.93 (two-sided log-rank test, $\alpha = 0.05$) to detect a difference if the underlying risk of death (hazard ratio) in the intraperitoneal group, as compared with the intravenous group, was 0.67. Survival was defined as the time from randomization to death from any cause.

Provisions for subgroup analysis were not included in the original study design. During the study, however, a consensus emerged among gynecologic oncologists that the patients most likely to benefit from intraperitoneal chemotherapy were those with a tumor mass that was no larger than 0.5 cm in the greatest dimension. Therefore, in January 1991, with no knowledge of subgroup data, we extended accrual for an additional year to achieve a sufficiently large sample for a separate analysis of data from patients with residual tumors that were no larger than 0.5 cm. All previously eligible patients were included in the extended sample, which was planned to include 560 eligible patients overall and 390 eligible patients with residual tumors no larger than 0.5 cm. In the analysis of this subgroup, if the hazard ratio was 0.67 for the patients receiving intraperitoneal treatment, the power to detect a difference was 0.88.

The treatment group, size of residual tumor (microscopical vs. ≤0.5 cm vs. >0.5 cm to 2 cm), age, performance status (0 or 1 vs. 2), race (white vs. other), tumor type (clear cell or mucinous vs. other), tumor grade, participating group (Southwest Oncology Group vs. Gynecologic Oncology Group vs. Eastern Cooperative Oncology Group), and timing of enrollment (during vs. after surgery) were included as covariates in Cox regression analyses.[10] Two-sided Fisher's exact tests were used for comparisons of toxic effects in the two treatment groups. All eligible patients who received chemotherapy were included in the analysis of toxicity.

RESULTS

Patients

Between June 1986 and July 1992, 654 women were randomly assigned to a study group: 295 from the Southwest Oncology Group, 298 from the Gynecologic Oncology Group, and 61 from the Eastern Cooperative Oncology Group. A total of 108 patients were ineligible (52 in the intravenous group and 56 in the intraperitoneal group) for the following reasons: inadequate surgery (in 54), pathological findings that did not meet the study criteria (31), insufficient documentation (20), and miscellaneous

TABLE 1. CHARACTERISTICS OF 546 ELIGIBLE PATIENTS WITH STAGE III OVARIAN CANCER WHO WERE ASSIGNED TO TREATMENT WITH INTRAVENOUS OR INTRAPERITONEAL CISPLATIN.*

CHARACTERISTIC	INTRAVENOUS GROUP (N=279)	INTRAPERITONEAL GROUP (N=267)
Age (yr)		
Median	56	59
Range	21–85	24–84
	% of patients	
White race	92	93
Minimal residual disease (≤0.5 cm)	72	73
No gross disease after initial surgery	26	25
Performance status of 0 or 1	86	85
Type of tumor		
Serous	66	67
Endometrioid	9	10
Mixed cell	6	6
Undifferentiated	11	11
Clear cell	2	2
Mucinous	3	1
Unknown	3	3
Tumor grade		
1	13	11
2	30	31
3	57	58
Postsurgical enrollment	94	94

*Of the 654 patients randomly assigned to treatment with intravenous cisplatin (331 patients) or intraperitoneal cisplatin (323), 108 were ineligible for the study (52 in the intravenous group and 56 in the intraperitoneal group).

TABLE 2. PERCENTAGES OF ELIGIBLE PATIENTS RECEIVING CISPLATIN AND THE DOSE RECEIVED DURING EACH COURSE OF TREATMENT.

TREATMENT COURSE	PATIENTS RECEIVING CISPLATIN		CISPLATIN DOSE RECEIVED	
	INTRAVENOUS GROUP	INTRAPERITONEAL GROUP	INTRAVENOUS GROUP	INTRAPERITONEAL GROUP
	% of patients		% of initial dose	
1	99	93	100	100
2	96	87	102	100
3	92	81	98	98
4	84	75	97	99
5	73	67	99	98
6	58	58	96	97

clinical factors that did not meet the study criteria (3). Table 1 shows the characteristics of the eligible patients. There were no significant differences between the study groups with respect to important prognostic factors.

Of the 279 eligible patients in the intravenous group, 2 died before treatment, and 1 refused treatment after randomization. There were 20 major protocol violations among the 267 eligible patients in the intraperitoneal group: 3 patients died before treatment was started, 6 withdrew consent after randomization, 8 did not receive the assigned treatment for other reasons (5 because of complications related to intraperitoneal catheterization and 3 because of errors by the local pathologist), 2 received treatment for only one day, and 1 erroneously received intravenous carboplatin during cycles 2 through 6. All 546 eligible patients were included in the efficacy analyses (according to the intention-to-treat principle), regardless of whether they completed the assigned treatment. The 20 patients in both groups who did not receive any treatment were excluded from the toxicity analysis.

Intensity of Cisplatin Dose

In both the intravenous and intraperitoneal groups, 58 percent of all eligible patients completed six courses of cisplatin therapy (Table 2). Among these patients, the average proportion of the initial cisplatin dose administered during cycle 6 (the course with the maximal dose reduction) was 96 percent in the intravenous group and 97 percent in the intraperitoneal group. Cisplatin was discontinued because of toxic effects (with a concomitant increase in the cyclophosphamide dose) in 40 patients in the intravenous group and 22 in the intraperitoneal group.

Complete Pathological Responses

Of the 546 eligible patients, 20 never received any study treatment, 81 did not complete therapy, and 45 had tumors that progressed before the completion of therapy. Second-look surgery was not required in these patients. In 103 of the remaining 400 patients, surgery was contraindicated or the patient refused it (70 patients), or the procedure was performed but deemed inadequate by the Gynecologic Surgical Review Board (33). Because of the bias associated with this group of 103 patients who had no clinical evidence of disease at the completion of therapy but did not undergo second-look surgery or had inadequate surgery, the rates of pathological responses are given without statistical comparisons.

A total of 297 patients with no clinical evidence of disease at the end of chemotherapy underwent adequate second-look surgery. The rate of complete pathological responses was 36 percent in the intravenous group (complete responses in 57 of 158 pa-

TABLE 3. SURVIVAL OF ALL ELIGIBLE PATIENTS, ELIGIBLE PATIENTS WITH MINIMAL RESIDUAL DISEASE, AND ALL RANDOMIZED PATIENTS.*

SURVIVAL	ALL ELIGIBLE PATIENTS		ELIGIBLE PATIENTS WITH MINIMAL RESIDUAL DISEASE		ALL RANDOMIZED PATIENTS	
	INTRAVENOUS GROUP (N=279)	INTRAPERITONEAL GROUP (N=267)	INTRAVENOUS GROUP (N=202)	INTRAPERITONEAL GROUP (N=195)	INTRAVENOUS GROUP (N=331)	INTRAPERITONEAL GROUP (N=323)
Survival (mo)						
Median	41	49	46	51	40	48
95% confidence interval	34–47	42–56	37–57	44–67	34–45	42–54
Hazard ratio	0.76†		0.80‡		0.77†	

*Minimal residual disease was defined as a residual tumor mass that was less than or equal to 0.5 cm in the greatest dimension.

†The hazard ratio is for the intraperitoneal group as compared with the intravenous group (P=0.02).

‡The hazard ratio is for the intraperitoneal group as compared with the intravenous group (P=0.10).

tients) and 47 percent in the intraperitoneal group (complete responses in 66 of 139).

Survival

All eligible patients were included in the primary analysis regardless of whether they completed the assigned treatment. Covariates associated with improved survival included the absence of gross disease at enrollment ($P<0.001$), a younger age ($P<0.001$), a type of tumor other than clear cell or mucinous ($P<0.001$), and enrollment after surgery ($P<0.001$). The final Cox model included these four factors and performance status (which was retained in the model because of its established prognostic importance).

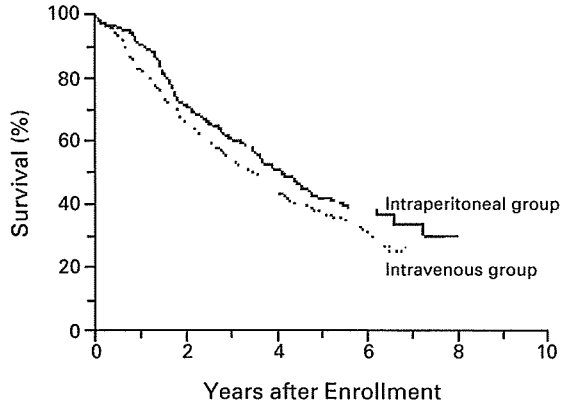
The results after adjustment for these five factors are shown in Table 3, along with unadjusted median survival in the two groups. The hazard ratio for the risk of death in the intraperitoneal group, as compared with the intravenous group, was 0.76 (95 percent confidence interval, 0.61 to 0.96; $P=0.02$). The median survival was 41 months (95 percent confidence interval, 34 to 47) in the intravenous group and 49 months (95 percent confidence interval, 42 to 56) in the intraperitoneal group (Fig. 1).

Figure 2 shows the survival curves for all eligible patients according to the extent of residual intraperitoneal disease. The effect of the treatment (intravenous or intraperitoneal cisplatin) was not influenced by the extent of residual disease ($P=0.93$ for the interaction of treatment and residual disease). Table 3 shows the results of a separate analysis for the subgroup of patients with residual tumors no larger than 0.5 cm. The analysis was repeated for all 654 randomized patients, including those who were ineligible. The results were equivalent to those of the primary analysis (Table 3).

Toxic Effects

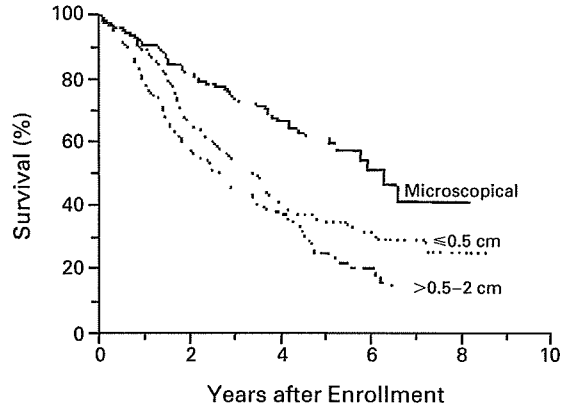
Two treatment-related deaths occurred in the intraperitoneal group. One patient died of respiratory failure of unknown cause 41 days after the second cycle of chemotherapy (blood counts were adequate at the time of death). The second patient died of bronchopneumonia during a period of chemotherapy-associated leukopenia 13 days after the third cycle. No treatment-related deaths occurred in the intravenous group.

Significantly more patients in the intravenous group than in the intraperitoneal group had grade 3 or higher granulocytopenia ($P=0.002$) and leukopenia ($P=0.04$) (Table 4). Table 5 shows the frequency of other toxic effects (grade 2 or higher) during any treatment cycle. Moderate-to-severe tinnitus and hearing loss were more frequent in patients receiving intravenous cisplatin than in those receiving intraperitoneal cisplatin. In addition, significantly more patients in the intravenous group had grade 2 or 3 neuromuscular toxic effects at the



Group	No. at Risk	No. of Deaths	Median Survival (mo)
Intraperitoneal	267	147	49
Intravenous	279	174	41

Figure 1. Survival of 546 Eligible Patients with Stage III Ovarian Cancer Who Were Randomly Assigned to Treatment with Intravenous or Intraperitoneal Cisplatin.



Residual Tumor	No. at Risk	No. of Deaths	Median Survival (mo)
Microscopical	139	53	76
≤0.5 cm	254	157	42
>0.5–2 cm	153	111	32

Figure 2. Survival of Eligible Patients According to the Extent of Residual Disease at Enrollment.

completion of chemotherapy (25 percent, vs. 15 percent in the intraperitoneal group; $P=0.02$).

As expected, abdominal pain of grade 2 or higher was more common in the intraperitoneal group ($P<0.001$); however, the pain usually resolved within 24 hours and was controlled with nonopioid or only weak opioid drugs. One patient had grade 4 abdominal pain. Transient dyspnea was infrequent but occurred in a significantly larger proportion of pa-

TABLE 4. FREQUENCY OF HEMATOLOGIC TOXIC EFFECTS (≥GRADE 3) DURING ANY COURSE OF TREATMENT.

TOXIC EFFECT	INTRAVENOUS GROUP (N=276)	INTRAPERITONEAL GROUP (N=250)	P VALUE
	% of patients		
Anemia (<8.0 g of hemoglobin/dl)	25	26	0.84
Granulocytopenia (<1000 granulocytes/mm³)	69	56	0.002
Leukopenia (<2000 white cells/mm³)	50	40	0.04
Thrombocytopenia (<50,000 platelets/mm³)	9	8	0.64

TABLE 5. FREQUENCY OF OTHER TOXIC EFFECTS (≥GRADE 2) DURING ANY COURSE OF TREATMENT.

TOXIC EFFECT*	INTRAVENOUS GROUP (N=276)	INTRAPERITONEAL GROUP (N=250)	P VALUE
	% of patients		
Abdominal pain	2	18	<0.001
Fever	5	6	0.45
Tinnitus	14	7	0.01
Hearing loss	15	5	<0.001
Neuromuscular effects	21	16	0.18
Neuromuscular effects at end of treatment†	25	15	0.02
Pulmonary effects	0.4	3	0.002

*Grade 2 toxic effects were defined as follows: abdominal pain was pain relieved by oral opioids; fever, a temperature higher than 38°C; tinnitus, moderate symptoms of tinnitus; hearing loss, the ability to hear normal voice and sound levels but not whispered sounds; neuromuscular effects, an absence of deep-tendon reflexes, weakness, and peripheral-nerve pain; and pulmonary effects, transient dyspnea on mild exertion.

†A total of 201 patients in the intravenous group and 175 in the intraperitoneal group completed five or six courses of treatment.

tients in the intraperitoneal group (3 percent, vs. 0.4 percent in the intravenous group; P=0.002). In the patients receiving intraperitoneal cisplatin, dyspnea probably resulted from compression of the base of the lung by the fluid-filled intraperitoneal cavity.

DISCUSSION

In this study we compared intraperitoneal with intravenous cisplatin in women with advanced ovarian cancer. All the patients had undergone debulking surgery and received intravenous cyclophosphamide concomitantly with the cisplatin. The median survival of the patients treated intraperitoneally was 8 months longer than that of the patients given intravenous cisplatin (49 vs. 41 months), and the hazard ratio in the intraperitoneal group was 0.76 (P=0.02). These results represent a 20 percent improvement in median survival and a 24 percent reduction in the risk of death during the entire follow-up period among the eligible patients in the intraperitoneal group.

Neutropenia, tinnitus, hearing loss, and neuromuscular toxic effects were significantly less frequent in the intraperitoneal group than in the intravenous group. Abdominal pain was more common in the intraperitoneal group, but in most cases it was transient and not severe (i.e., grade 3 or higher in only 5 percent of the patients).

Previous reports have summarized the toxic effects of intraperitoneal cisplatin at doses ranging from 50 to 100 mg per square meter.[11-13] Chronic, low-grade inflammation from repeated intraperitoneal administration may cause mild-to-severe abdominal pain and intraabdominal adhesions. These reports have generally focused on patients who had undergone two exploratory laparotomies before the administration of intraperitoneal cisplatin. In our study, all the patients had undergone only one definitive exploratory laparotomy within four weeks before the start of chemotherapy. Thus, our patients were probably less susceptible to the local toxic effects of intraperitoneal cisplatin.

Howell et al. reported that after second-line therapy with intraperitoneal cisplatin, rates of surgically established complete responses were significantly higher among patients with smaller residual intraperitoneal tumor masses (≤0.5 cm) than among those with larger masses (>0.5 cm to 2 cm).[8] Consistent with this finding was the 80 percent rate of a complete pathological response among our patients with no gross residual disease who received intraperitoneal cisplatin (32 of 40 patients), as compared with a rate of 56 percent among those with no gross residual disease who received intravenous cisplatin (24 of 43). Such results reflect the fact that the penetration of intraperitoneal cisplatin is limited to a depth of 0.1 to 1 mm from the surface of the peritoneal tumor.[14]

We found that intraperitoneal cisplatin was associated with a longer survival than was intravenous cisplatin, whether residual intraperitoneal tumor masses were 0.5 cm or less or more than 0.5 cm in the greatest dimension. We do not know the reason for this result, but several explanations are possible. All previous investigations of intraperitoneal cisplatin therapy have been phase 2 studies, which included mainly patients who had already received intravenous cisplatin. Our patients had never before received chemotherapy, and their tumors may therefore have been highly sensitive to cisplatin. Moreover, the precision in measuring intraperitoneal tumor masses during an initial exploratory laparotomy is limited, and the total volume of the mass may

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have more prognostic value than the maximal dimension.

The combination of intravenous paclitaxel plus intraperitoneal cisplatin may prove to be more effective than intravenous cyclophosphamide plus intraperitoneal cisplatin in patients with stage III ovarian cancer and minimal residual disease. The Gynecologic Oncology Group recently reported that paclitaxel plus cisplatin significantly increased survival (median, 38 months, vs. 24 months with cyclophosphamide plus cisplatin) when administered as primary chemotherapy in women with incompletely resected stage III or IV ovarian cancer.[15] Ongoing phase 3 studies by the Gynecologic Oncology Group and the Southwest Oncology Group will further define the role of intraperitoneal cisplatin (and intravenous paclitaxel) in the treatment of stage III ovarian cancer that has been optimally resected.

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Phase III Trial of Standard-Dose Intravenous Cisplatin Plus Paclitaxel Versus Moderately High-Dose Carboplatin Followed by Intravenous Paclitaxel and Intraperitoneal Cisplatin in Small-Volume Stage III Ovarian Carcinoma: An Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group

By Maurie Markman, Brian N. Bundy, David S. Alberts, Jeffrey M. Fowler, Daniel L. Clark-Pearson, Linda F. Carson, Scott Wadler, and Joshua Sickel

Purpose: To compare the progression-free and overall survival in small-volume residual ovarian cancer after treatment with intravenous (IV) cisplatin and paclitaxel or an experimental regimen of IV carboplatin followed by IV paclitaxel and intraperitoneal cisplatin.

Patients and Methods: Patients were randomized to receive either IV paclitaxel 135 mg/m^2 over 24 hours followed by IV cisplatin 75 mg/m^2 every 3 weeks for six courses or IV carboplatin (area under curve 9) every 28 days for two courses, then IV paclitaxel 135 mg/m^2 over 24 hours followed by intraperitoneal (IP) cisplatin 100 mg/m^2 every 3 weeks for six courses.

Results: Of the 523 patients who entered this trial, 462 were determined to be assessable, with prognostic factors well balanced between the treatments. Neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities were greater in the experimental arm. As a result, 18% of the patients received ≤ two courses of IP therapy. Progression-free survival was superior for patients randomized to the experimental treatment arm (median, 28 v 22 months; relative risk, 0.78; log-rank $P = .01$, one-tail). There was a borderline improvement in overall survival associated with this regimen (median, 63 v 52 months; relative risk, 0.81; $P = .05$, one-tail).

Conclusion: An experimental regimen including moderately high-dose IV carboplatin followed by IP paclitaxel and IV cisplatin yielded a significant improvement in progression-free survival when compared with a standard regimen of IV cisplatin and paclitaxel. Because the improvement in overall survival was of borderline statistical significance and toxicity was greater, the experimental arm is not recommended for routine use. However, the results provide direction for further clinical investigation in small-volume ovarian cancer.

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CURRENT STANDARD management of advanced ovarian cancer includes the administration of a platinum agent in combination with paclitaxel.[1,2] Despite the demonstrated clinical utility of this combination chemotherapy strategy, the majority of women who present with ovarian cancer in its advanced stages ultimately die of complications of the malignancy. Thus there remains a critical need to examine innovative strategies that may ultimately impact on outcome in this disease.

Preclinical data and phase II clinical studies have suggested the potential utility of giving cisplatin by the intraperitoneal (IP) route, and a recently reported phase III intergroup trial has shown a survival advantage for this approach in the management of small-volume residual ovarian cancer.[3,4]

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The concept of employing systemically administered cytotoxic agents to chemically debulk residual cancer before regional drug delivery has been hypothesized to optimize the benefits of IP therapy by reducing the size of any residual tumor nodules to less than that which can be accomplished surgically.[5] To test the potential clinical advantage of combining systemic chemical debulking with IP cisplatin in patients also receiving intravenously (IV) administered paclitaxel, the Gynecologic Oncology Group (GOG), Southwest Oncology Group, and the Eastern Cooperative Oncology Group (ECOG) initiated a randomized, controlled phase III trial of standard-dose IV cisplatin/paclitaxel for six courses,[1] compared with an experimental regimen of two cycles of moderately high-dose single-agent carboplatin, area under curve (AUC) 9, followed by six courses of IP cisplatin and IV paclitaxel. We report here the results of this study.

PATIENTS AND METHODS

Eligibility Criteria

Patients considered for entry onto this randomized trial had to meet all of the following eligibility criteria: (1) histologic diagnosis of epithelial ovarian carcinoma, stage III (histologic types permitted: serous, mucinous, clear-cell, and endometrioid adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's tumor, and adenocarcinoma not otherwise specified [NOS]); (2) presence of optimal residual disease (largest residual tumor nodule $\leq$ 1 cm in maximal diameter) at the completion of staging and tumor debulking; (3) entry onto the study within 6 weeks of surgery; (4) adequate bone marrow (WBC $\geq$ 3,000 cells/mm^3, platelets $\geq$ 100,000/mm^3), renal (creatinine clearance $\geq$ 50 mL/min), and hepatic (bilirubin $\leq$ 1.5 times normal, serum AST $\leq$ three times normal function; (5) GOG performance status of 0, 1, or 2; and (6) signed, approved informed consent document stating they understood the investigational nature of the treatment program before entry onto study.

Patients considered ineligible for entry into this protocol included (1) those with ovarian carcinoma of low malignant potential (borderline tumors); (2) patients with suboptimal residual IP (> 1 cm largest residual tumor nodule) or stage IV disease; (3) patients who had previously received chemotherapy or radiotherapy; (4) patients with septicemia, severe infection, acute hepatitis, or severe gastrointestinal bleeding; (5) GOG performance status of 3 or 4; (6) patients with a past or concomitant malignancy other than skin cancer (excluding melanoma); or (7) patients with a history of congestive heart failure or unstable angina or those who had a myocardial infarction within the past 6 months. Patients who were not expected to tolerate the hemodynamic effects of sinus bradycardia, individuals with evidence of abnormal cardiac conduction, and patients taking medications known to affect the cardiac conduction system were also not eligible.

Treatment Regimens

The study was originally designed as a three-arm trial, the third arm being a regimen of cisplatin 75 mg/m^2 and cyclophosphamide 750 mg/m^2. When the initial results of GOG Trial #111 became available, in which it was demonstrated that in suboptimal residual ovarian cancer the combination of cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 delivered over 24 hours resulted in a superior response rate and progression-free survival compared with the identical cisplatin and cyclophosphamide regimen being used in the current trial,[1] the cisplatin/cyclophosphamide arm of the study was discontinued. Because only 66 patients were enrolled to receive the cisplatin/cyclophosphamide regimen, there are no definitive conclusions regarding efficacy of paclitaxel forthcoming from this part of the trial. Therefore, this study arm will not be discussed further in this report. The two completed study arms included the following: regimen 1, paclitaxel 135 mg/m^2 by continuous IV infusion for 24 hours on day 1 followed by cisplatin 75 mg/m^2 IV on day 2, every 21 days for six courses; regimen 2, carboplatin (AUC 9) IV for two courses every 28 days, followed 4 weeks later by paclitaxel 135 mg/m^2 by continuous IV infusion over 24 hours on day 1, followed by cisplatin 100 mg/m^2 IP on day 2, every 21 days for six courses. The carboplatin dose was calculated based on the formula of Calvert et al[6] with the glomerular filtration rate being considered to be equivalent to the creatinine clearance. The creatinine clearance was calculated by the method of Jelliffe.[7] The IP cisplatin was delivered in 2 L of normal saline through an implantable peritoneal dialysis catheter (ie, Tenckhoff catheter) which was permitted to be connected to an indwelling port. If it was not possible to deliver cisplatin by the IP route because of a malfunction of the catheter, cisplatin was administered IV at a reduced dose of 75 mg/m^2 to complete the six treatment courses.

Decisions regarding antiemetics and specific hydration programs for cisplatin were left to the discretion of the individual treating physicians. All patients received prophylaxis for the prevention of paclitaxel-associated hypersensitivity reactions (dexamethasone, diphenhydramine, and either cimetidine or ranitidine).

Treatment Modifications

To maintain a consistent dose-intensity in the study, there were no dose reductions in the protocol. Treatment was to be delayed week to week until minimum hematologic, renal, and other parameters were met. Treatment delays were to be kept to a minimum, and every effort was made to maintain the planned schedule. Delays were not permitted other than for documented toxicity.

Subsequent treatments were not to begin until the WBC was $\geq$ 3,000 cells/mm^3 and the platelet count was $\geq$ 100,000/mm^3. Patients developing grade 3 or 4 peripheral neuropathy were to have treatment interrupted until the adverse effects had resolved to a maximum of grade 1.

Evaluation Criteria

Because all individuals entered onto this protocol had IP disease $\leq$ 1 cm in maximal diameter, no patient had measurable tumor masses. A second-look surgical procedure was planned to be performed in all patients without evidence of progressive disease within 8 weeks after the last course of chemotherapy. Patients who exhibited progression of disease during treatment or before the performance of the second-look laparotomy were not expected to undergo this diagnostic procedure. Negative surgical pathologic findings at second-look surgery were to have been an end point, but the frequency of not having the second-look procedure was sufficiently high and disproportionate between the two treatment groups to render this end point unreliable and likely biased. For this reason, progression-free survival (PFS) and overall survival are the end points of this study. Survival time was defined as the observed length of life from entry into the protocol to death, or, for

living patients, date of last contact (regardless of whether this contact was on a subsequent protocol). PFS was defined as the date from entry onto the protocol to the date of appearance of disease (clinically or radiologically detected, not surgically), or PFS was equal to the survival time in the absence of disease.

Statistical Considerations

Randomization with equal probability of assignment to each treatment regimen was carried out by a block arrangement balancing the treatment assignment within gross residual disease status (categories: Yes and No) and major GOG institutions. The accrual goal was set at 440 eligible patients and follow-up until 150 deaths occur. This sample size would provide a statistical power of 80% to detect a proportional one-third decrease in the hazards rate when testing at .05 level (one-sided test).[8] This report includes 233 deaths, which far exceeds the original goal, and therefore, provides 80% statistical power to detect a 28% reduction in the hazards rate. This difference is on par with the mortality reduction observed in SWOG 8501 (GOG 104) for the entire study group of 24%.

Life tables were computed by using the method of Kaplan and Meier.[9] Differences in PFS and survival by treatment were evaluated by using the log-rank test[10] according to the intent-to-treat principle of eligible patients. Treatment effect on PFS and survival while adjusting for prognostic factors was accomplished by using the Cox model.[11] Screening for chance imbalances between clinical/pathologic characteristics and treatment assignment was accomplished by using the Pearson's χ^2 test significance level of .20.[12] The Mann-Whitney U test was used when the characteristic was continuous (eg, age).[12]

RESULTS

Patient Characteristics

From August 1992 until April 1995, a total of 523 patients were entered onto the two arms of this randomized trial, of whom 61 (11.7%) were subsequently considered to be ineligible (33 in the platinum/paclitaxel arm, 28 in the carboplatin/IP cisplatin/paclitaxel arm). Reasons for patient exclusion, which did not differ between the study regimens, included wrong stage (n = 18), inadequate surgery (n = 13), low malignant potential tumor (n = 11), gross residual disease more than 1 cm (n = 7), wrong primary (n = 6), second primary cancer (n = 2), wrong cell type (n = 2), and inadequate pathology (n = 2).

Of the 462 eligible patients, the treatment groups were well balanced regarding age, race, GOG performance status, histologic subtype of ovarian cancer, tumor grade, and residual disease status (Table 1). Table 2 shows the percentage of patients receiving different numbers of treatment cycles. Of note, 6.8% of the patients randomized to the experimental arm did not receive any IP therapy, whereas 18.3% of the patients on this regimen received two courses or less of IP drug delivery, principally because of excessive bone marrow toxicity encountered during the initial cycles of IV carboplatin.

Table 1. Clinical and Pathologic Features by Treatment Group

Characteristic	IV Cisplatin IV Paclitaxel (n = 227)		Carboplatin/IP Cisplatin/IV Paclitaxel (n = 235)	
	No. of Patients	%	No. of Patients	%
Age				
< 51 years	85	37	77	33
51-60 years	61	27	76	32
61-70 years	54	24	60	26
> 70 years	27	12	22	9
Race				
White	202	89	215	91
Black	16	7	14	6
Other	9	4	6	3
GOG performance status				
0	99	44	106	45
1	104	46	106	45
2	24	11	23	10
Cell type				
Serous adenocarcinoma	159	70	149	63
Endometrioid	22	10	32	14
Mixed epithelial	21	9	22	9
Other*	25	11	32	14
Tumor grade				
1	32	14	25	11
2	91	40	92	39
3	104	46	118	50
Residual tumor status				
Microscopic	82	36	82	35
Gross residual	145	64	153	65

*Includes adenocarcinoma-NOS, clear cell, mucinous, undifferentiated, and transitional cell carcinoma.

Toxicity

Table 3 outlines the major toxicities encountered by patients treated on the two arms of this randomized trial. There was significantly more grade 4 neutropenia and grade 3-4 thrombocytopenia in the experimental arm. Grade 3-4 gastrointestinal and metabolic toxicity was also greater in patients receiving this therapeutic regimen.

Two patients from each regimen died of causes considered to be related to chemotherapy. In the control arm, both patients had a grade 4 gastrointestinal toxicity, with one also having grade 4 hematologic toxicity. In the experimental arm, both deaths were associated with grade 4 hematologic toxicity.

Second-Look Results

The frequency of refusal for the performance of second-look surgical procedures was higher than expected and imbalanced between the two regimens (IV regimen, 15.0% *v* IP regimen, 22.6%). A treatment comparison of the frequency of pathologically negative findings in the subset

Table 2. Courses of Chemotherapy Administered

Number of Courses	IV Cisplatin IV Paclitaxel		Carboplatin/IP Cisplatin/IV Paclitaxel	
	No. of Courses	%	No. of Courses	%
Carboplatin				
0		—	3	1
1		—	6	3
2		—	225	96
3		—	1	0
Cisplatin/paclitaxel				
0	4	2	16	7*
1	6	3	15	6
2	5	2	12	5
3	4	2	9	4
4	4	2	4	2
5	8	4	12	5
6	196	86	167	71

NOTE. Some percentages do not add up to 100% because of rounding.
*Includes three patients who received no chemotherapy, three patients who received one course of carboplatin, and 10 patients who received both courses of carboplatin.

of individuals undergoing surgery is likely biased. Therefore, this study end point was not examined further.

PFS

At the time of this report, 56 patients (24.7%) randomized to the control arm have no evidence of disease, compared with 75 individuals (31.9%) on the experimental arm. Nine and 10 of these patients who died without documented disease recurrence were in the standard IV therapy regimen and IP arm, respectively.

PFS was found to be longer in the experimental arm, with a median time to recurrence of 27.9 months compared with 22.2 months in the standard cisplatin/paclitaxel arm (log-rank $P = .01$, one-tail) (Fig 1). The relative risk estimate of the experimental arm to the control was 0.78 (90% confidence interval [CI], 0.66 to 0.94). When adjusting for statistically significant prognostic factors, ie, gross residual disease status, cell type (high risk: mucinous, clear-cell, adenocarcinoma-NOS) and histologic grade, the relative risk estimate decreased only slightly (ie, 0.75).

Overall Survival

At the time of analysis, 103 patients (45.4%) on the standard arm remain alive, compared with 126 (53.6%) randomized to the experimental regimen. There was a borderline significant improvement in survival for the experimental arm with a median time to death of 63.2 months compared with 52.2 months in the standard cisplatin/paclitaxel arm (log-rank $P = .05$, one-tail) (Fig 2). The relative risk estimate of the experimental arm to the control was 0.81 (90% CI, 0.65 to 1.00). When adjusting for statistically significant prognostic factors of gross residual disease status, cell type (high risk: mucinous, clear-cell, adenocarcinoma-NOS) and age, the relative risk estimate decreased only slightly (ie, 0.78).

DISCUSSION

When the present study was being planned, it was recognized that a better result for the experimental arm would not give a clear answer about IP cisplatin separate from the effect of IV carboplatin, and vice versa. Rather, it was hoped that a major advancement in the management of ovarian cancer might be achieved by combining these two strategies. The actual outcome has been a modest advance, with a significant improvement in PFS and borderline significant improvement in survival, but with greater toxicity. The question arises about future directions that can be gleaned from this study.

Table 3. Patients Experiencing Grade 3 and 4 Toxicity

Toxicity	IV Cisplatin IV Paclitaxel (n = 227)				Carboplatin/IP Cisplatin/IV Paclitaxel (n = 235)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
WBC	111	49	29	13	114	49	66	28
Platelets	4	2	2	1	59	25	56	24
Other hematologic	23	10	178	78	29	12	189	80
Gastrointestinal	21	9	19	8	40	17	46	20
Cardiovascular	5	2	1	< 1	7	3	1	< 1
Neurologic	19	8	1	< 1	24	10	4	2
Infection	3	1	1	< 1	10	4	1	< 1
Metabolic	1	< 1	2	1	16	7	7	3
Creatinine clearance	2	1	1	< 1	6	3	4	2
Fever	2	1	1	< 1	5	2	2	1
Allergic reaction	2	1	2	1	0	0	0	0
Fatigue	3	1	0	0	6	3	1	< 1

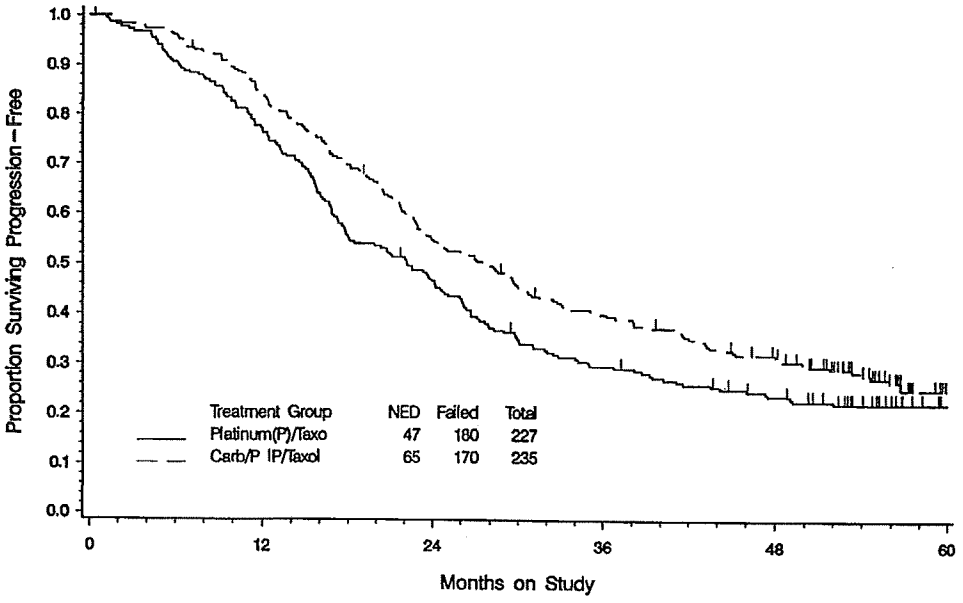

Fig 1. Progression-free survival ($P = .01$).

It had been hypothesized previously that the high local concentrations of cisplatin achievable within the peritoneal cavity after regional administration (10- to 20-fold greater than measured within the systemic compartment) would exert its maximum benefit in patients with microscopic residual disease or very small-volume macroscopic cancer at the time of IP drug delivery.[3] Support for this concept comes from preclinical data where the depth of penetration of cytotoxic agents directly into tumor or normal tissue after regional delivery has been measured in millimeters or less from the surface of the peritoneal lining.[13-15] Similarly, a number of phase II efficacy trials of IP therapy examined in the salvage setting in women with ovarian cancer have revealed that responses are almost exclusively observed in individuals with microscopic disease only or in those individuals whose maximal tumor diameter measures less than 0.5 to 1 cm.[3,16-18]

Consideration of these preclinical and clinical data led to the proposal that two courses of moderately dose-intensive

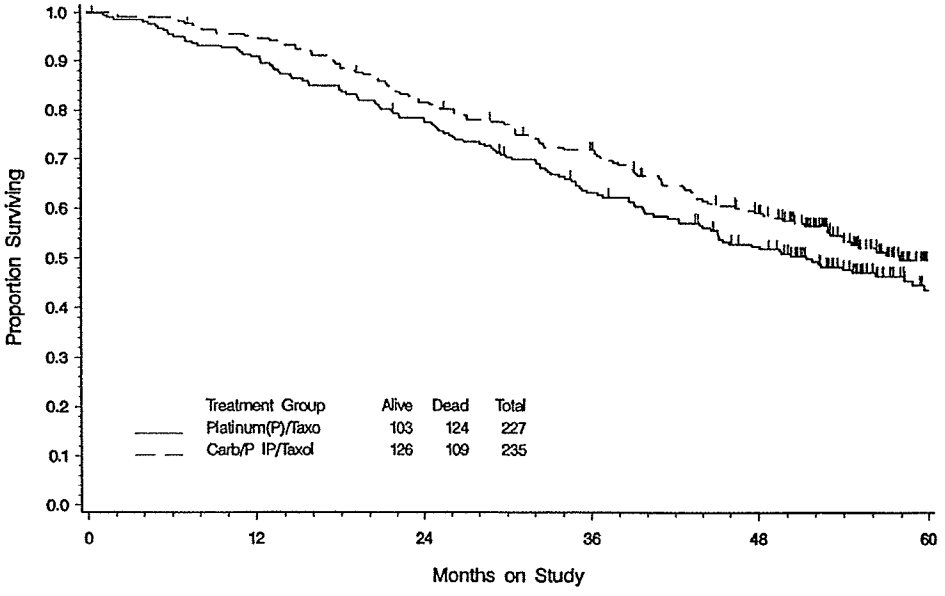

Fig 2. Overall survival ($P = .05$).

systemic chemotherapy (eg, carboplatin [AUC 9]) might be able to rapidly reduce the volume of residual cancer persisting within the abdominal cavity after maximal surgical cytoreduction. This reduction in tumor volume might then improve the chances that additional treatment with cisplatin delivered regionally would favorably influence outcome in this malignancy. This concept of chemical debulking before the regional delivery of cisplatin had previously been examined in a pilot study using cisplatin, rather than carboplatin, as the initial systemic treatment regimen.[5] It might be tempting to speculate that the favorable results associated with the experimental study arm in this study were due, at least in part, to the two courses of moderately high-dose carboplatin administered before IP cisplatin and IV paclitaxel. Several randomized trials have now definitively established that doubling the dose-intensity of platinum agents in the management of ovarian cancer results in increased toxicity (as observed in our trial) without any evidence of an improvement in response rate or survival.[19-21] However, these studies do not address the benefit in outcome when substantially increasing the total dose. A study by Kaye et al[22] that doubled the intensity and the total dose of cisplatin demonstrated a relative death rate of 0.68 (95% CI, 0.46 to 0.99) in favor of the high-dose regimen.

At this juncture, what should we consider the status of IP cisplatin as initial therapy of small-volume residual advanced ovarian cancer? Despite the favorable impact of the regional strategy as demonstrated in this trial, it is not appropriate to suggest that this regimen should be used in standard clinical practice.

The toxicity of the carboplatin regimen, particularly when followed by IP cisplatin and IV paclitaxel, was considerable. In addition, although an improvement in PFS was observed, the impact on overall survival in this clinical setting was only marginal. Given the mature results of this large randomized multi-institutional phase III clinical trial, it is reasonable to draw several conclusions. First, this study has confirmed the previously documented relative safety of administering IP cisplatin to patients with small-volume residual advanced ovarian cancer outside the clinical research center setting.[4] Second, the results of this study support the conclusions of a previously reported randomized trial examining IP cisplatin in women with stage III ovarian cancer. This previous intergroup phase III trial demonstrated a survival advantage associated with the use of IP cisplatin compared with IV cisplatin delivery, both in combination with systemic cyclophosphamide.[4] The experimental arm in this trial resulted in an improvement in PFS (relative risk of 0.78) compared with IV administration. Although the survival difference in this trial is only of borderline statistical significance, the relative risk of 0.81 is remarkably consistent with the relative risk of 0.80 for the minimal residual-disease subgroup (ie, $\leq$ 0.5 cm) from the previous intergroup study.

Third, further exploration of a role for IP chemotherapy in the management of this malignancy is indicated by the positive results of this and other studies. It is now known that the administration of cisplatin plus paclitaxel results in a superior outcome (objective response rate, PFS, overall survival) compared with treatment with cisplatin and cyclophosphamide.[1,2] Therefore, it is important to determine whether the regional pharmacokinetic advantage associated with the IP delivery of cisplatin can translate into additional clinical benefit when the drug is combined with paclitaxel.

The GOG has initiated a second IP chemotherapy trial based on the results of this trial and data demonstrating that paclitaxel can be delivered safely into the peritoneal cavity with both a major pharmacokinetic advantage for cavity exposure[23,24] and evidence of considerable activity in individuals with microscopic residual ovarian cancer after initial IV chemotherapy.[25] The currently active GOG trial for patients with optimal residual advanced ovarian cancer examines the combination of IP cisplatin and paclitaxel, along with IV paclitaxel, compared with standard IV delivery of the two cytotoxic agents.

APPENDIX

The following institutions participated in this study: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University School of Medicine, University of Minnesota Medical School, University of Southern California Medical Center at Los Angeles, University of Mississippi Medical Center, Colorado Foundation for Medical Care, University of California Medical Center at Los Angeles, University of Washington Medical Center, Hospital of the University of Pennsylvania, University of Miami School of Medicine, The Milton S. Hershey School of Medicine of the Pennsylvania State University, Georgetown University Hospital, University of Cincinnati College of Medicine, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University Medical Center, Wake Forest University School of Medicine, The Albany Medical College of Union University, University of California Medical Center at Irvine, Tufts New England Medical Center, Rush-Presbyterian-St. Lukes Medical Center, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, The Johns Hopkins Oncology Center, State University of New York at Stony Brook,