Randomized Intergroup Trial of Cisplatin–Paclitaxel Versus Cisplatin–Cyclophosphamide in Women With Advanced Epithelial Ovarian Cancer: Three-Year Results

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Background: A randomized trial conducted by the Gynecologic Oncology Group (GOG, study #111) in the United States showed a better outcome for patients with advanced ovarian cancer on the paclitaxel–cisplatin regimen than for those on a standard cyclophosphamide–cisplatin regimen. Before considering the paclitaxel–cisplatin regimen as the new “standard,” a group of European and Canadian investigators planned a confirmatory phase III trial. Methods: This intergroup trial recruited 680 patients with broader selection criteria than the GOG #111 study and administered paclitaxel as a 3-hour instead of a 24-hour infusion; progression-free survival was the primary end point. Patient survival was analyzed by use of the Kaplan–Meier technique. Treatment effects on patient survival were estimated by Cox proportional hazards regression models. All statistical tests were two-sided. Results: The overall clinical response rate was 59% in the paclitaxel group and 45% in the cyclophosphamide group; the complete clinical remission rates were 41% and 27%, respectively; both differences were statistically significant ($P = .01$ for both). At a median follow-up of 38.5 months and despite a high rate of crossover (48%) from the cyclophosphamide arm to the paclitaxel arm at first detection of progression of disease, a longer progression-free survival (log-rank $P = .0005$; median of 15.5 months versus 11.5 months) and a longer overall survival (log-rank $P = .0016$; median of 35.6 months versus 25.8 months) were seen in the paclitaxel regimen compared with the cyclophosphamide regimen. Conclusions: There is strong and confirmatory evidence from two large randomized phase III trials to support paclitaxel–cisplatin as the new standard regimen for treatment of patients with advanced ovarian cancer. [J Natl Cancer Inst 2000;92:699–708]

By mid-1993, the Gynecologic Oncology Group (GOG) had disclosed the first results of a prospective randomized clinical trial. In this trial, paclitaxel (T) (Taxol®; Bristol-Myers Squibb, Princeton, NJ), combined with cisplatin (P; given in 1 hour)—combination denoted as TP—was infused in patients with advanced ovarian cancer for a 24-hour period. This regimen produced a higher response rate and a longer progression-free survival (PFS) in women with newly diagnosed and suboptimally debulked International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer than those produced by the “standard” cyclophosphamide–cisplatin (CP) regimen (1).

A group of European and Canadian investigators found these results to be impressive but not conclusive enough. They believed that (a) further data were required before the TP combination could be adopted as the new standard first-line chemotherapy regimen for this disease, (b) the TP regimen could be improved by increasing the dose of paclitaxel and shortening its infusion time, and (c) more knowledge was needed regarding the comparative quality-of-life and economic impacts of these competing regimens.

As of April 1, 1994, the investigators from the European Organization for Research and Treatment of Cancer (EORTC), the Nordic Gynecological Cancer Study Group (NOCOVA), the National Cancer Institute of Canada Clinical Trials Group (NCI-CTG), and the Scottish group joined forces to seek a target accrual of 600 eligible patients. This level of accrual gave this study an 80% probability of detecting an increase in the median PFS by one third. Accrual of patients in the trial was completed in August 1995, 4 months after GOG publicly reported a highly significant survival advantage in favor of TP and 4 months before these striking results were published in the New England Journal of Medicine (2).
Patients

To be eligible for this study, patients had to have histologically verified epithelial ovarian carcinoma and FIGO stage IIB, IIC, III, or IV disease. Women had to have their initial surgical procedure within less than 8 weeks of recruitment, and their initial surgical procedure could have consisted of an optimal (=1-cm residual mass) or a suboptimal (>1-cm residual mass) tumor cytoreduction. Informed consent was obtained from all patients according to the requirements of local human biomedical ethics committees.

Patients were excluded if they displayed one of the following characteristics: a World Health Organization (WHO) performance status of 4; inadequate bone marrow function, defined as a neutrophil count less than $1.5 \times 10^9$/L and/or a platelet count less than $100 \times 10^9$/L; inadequate liver function, defined by bilirubin levels of more than $25 \mu$mol/L; or inadequate renal function, defined as a serum creatinine level greater than $134 \mu$mol/L in a patient weighing 45 kg or more or greater than $115 \mu$mol/L in a patient weighing less than 45 kg, unless the measured creatinine clearance under these circumstances would be greater than 60 mL/minute per 1.73 m².

Other exclusion criteria included the following: any previous chemotherapy or radiotherapy; complete bowel obstruction or presence of brain metastases; borderline ovarian tumors or abdominal carcinomas of unknown origin; a history of medically significant atrial or ventricular arrhythmias; congestive heart failure, even if medically controlled; a documented myocardial infarction within the 6 months preceding randomization; a second malignant disease (with the exception of basal cell carcinoma of the skin); expected inadequacy of follow-up; or active infection or serious other underlying medical conditions that would impair the ability of the patient to receive protocol treatment (including prior allergic reactions to drugs containing Cremophor®EL [polyoxyethylated castor oil]).

Clinical Trial Design

The clinical trial flow diagram is illustrated in Fig. 1. Patients were randomly assigned through one of four randomization sites: the EORTC Data Center in Brussels, Belgium; the Odense University Hospital in Odense, Denmark; the NCI-C-CTG headquarters in Kingston, ON, Canada; or the Scottish Group Data Center in Glasgow, U.K. (Beatson Oncology Center). Since the EORTC was the coordinating group for this study, eligibility checklists and treatment assignments were sent to the EORTC Data Center.

Patients were randomly assigned to receive the TP regimen (paclitaxel at a dose of 175 mg/m² as a 3-hour infusion followed by cisplatin at a dose of 75 mg/m²) or the CP regimen (cyclophosphamide at 750 mg/m² followed by cisplatin at 75 mg/m²). Stratification factors included the treating institution, the FIGO stage (IIB–C, III, or IV), the amount of residual disease (none or microscopic, ≤1 cm, or >1 cm), the WHO performance status (0–1, 2, or 3), and the tumor grade (well differentiated, moderately well differentiated, poorly differentiated, or missing, not applicable). A total of 680 patients were recruited in the trial.

After three cycles of therapy, a formal assessment had to be made, and patients had to be categorized with regard to their current disease status. By use of clinical and/or radiologic assessment, the patients were assigned to one of four subgroup categories: those who “progressed clinically” or who were “unchanged clinically” and those who showed “partial clinical response” or “complete clinical response.” For those patients undergoing interval debulking surgery, the subcategories were “progressed surgically,” “unchanged surgically,” those showing “partial surgical response” (referring to the status before interval debulking), or those showing “complete surgical response, pathologically documented” (again referring to the status before interval debulking). Of note, CA 125 measurements, if available, played no part in this assessment, with the exception of the complete response status, which required CA 125 normalization.

Patients categorized as “progressed clinically” or “progressed surgically” finished the protocol treatment and were allowed to receive any secondary treatment (including taxanes) at the investigators’ discretion. All of the other patients were scheduled to receive three further cycles of protocol treatment unless there was an overt clinical progression, the patient withdrew, or a medical contraindication appeared during this period.

After six cycles of protocol treatment, the patients had to be categorized with regard to their final response status with the use of clinical/radiologic assessments and/or second-look surgery assessment and the same subcategories as defined above. Patients not showing disease progression at this point could cease all cytotoxic therapy or could receive three additional cycles of protocol treatment.

While on protocol therapy, patients underwent the following procedures: symptom recording and physical examination every 3 weeks, complete blood cell counts weekly for the first two cycles and every 3 weeks thereafter, and laboratory tests of blood and CA 125 measurements (optional for Canadian centers) on day 1 of each cycle.

Radiologic investigations to document the status of all measurable lesions noted at baseline had to be repeated after three, six, and nine cycles of chemotherapy. Once patients were off the protocol therapy, they were monitored for assessment of disease status every 3 months for 2 years and every 6 months thereafter. Monitoring comprised clinical examination and CA 125 estimation; routine computed tomography scans were not required but were requested if the CA 125 level rose and/or symptoms developed.

Fig. 1. Flow diagram for evaluation of paclitaxel–cisplatin (TP) versus cyclophosphamide–cisplatin (CP) drug regimens in randomized clinical trial of patients with advanced ovarian cancer.

Advanced epithelial ovarian cancer FIGO stages IIb, III, IV

**Optimal (≤ 1 cm) and suboptimal (> 1 cm) residuum**

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
<th>N = 680</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment arms</strong></td>
<td></td>
</tr>
<tr>
<td>No patients (%)</td>
<td></td>
</tr>
<tr>
<td>– randomized</td>
<td>338 (100)</td>
</tr>
<tr>
<td>– fully eligible</td>
<td>330 (98)</td>
</tr>
<tr>
<td>– who started</td>
<td>336 (99)</td>
</tr>
<tr>
<td><strong>protocol treatment</strong></td>
<td></td>
</tr>
<tr>
<td>– who underwent</td>
<td></td>
</tr>
<tr>
<td>• interval debulking surgery</td>
<td>22 (7)</td>
</tr>
<tr>
<td>• second look surgery</td>
<td>68 (20)</td>
</tr>
<tr>
<td>– who completed protocol therapy</td>
<td>267 (79)</td>
</tr>
<tr>
<td>– who did not complete protocol therapy</td>
<td>71 (21)</td>
</tr>
<tr>
<td>• for progression</td>
<td>47</td>
</tr>
<tr>
<td>• for toxicity</td>
<td>15</td>
</tr>
<tr>
<td>– who started a new therapy without evidence of progression</td>
<td>14 (4)</td>
</tr>
<tr>
<td>– randomized</td>
<td>342 (100)</td>
</tr>
<tr>
<td>– fully eligible</td>
<td>338 (99)</td>
</tr>
<tr>
<td>– who started</td>
<td>339 (99)</td>
</tr>
</tbody>
</table>

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Chemotherapy Administration

TP and CP could be given either as inpatient or outpatient regimens. Details on drug administration are summarized in Table 1. Of note, polyvinylchloride-containing intravenous infusion sets could not be used for paclitaxel administration. In-line filtration of the prepared solution with the use of cellulose acetate filters of 0.22-μm pore size was mandatory during the paclitaxel infusion. Cardiac monitoring was not required, but vital signs had to be followed closely. Treatment cycles were repeated every 3 weeks, provided the neutrophil count was equal to or more than 1.5 × 10^9/L, the platelet count was equal to or more than 100 × 10^3/L, and toxic effects were not prohibitive. The protocol stipulated that a dose escalation of paclitaxel from 175 to 200 mg/m^2 had to be done with the second cycle of treatment in all patients who did not experience febrile neutropenia (defined as a temperature ≥38°C concomitant with a grade 4 neutropenia or severe prolonged myelosuppression, i.e., grade 4 neutropenia and/or grade 4 thrombocytopenia on two successive weekly counts) in the TP arm.

For patients who did experience the previously defined adverse hematologic toxic reaction, a 20% reduction in the paclitaxel or cyclophosphamide dosages was planned, with no reduction in the cisplatin dose. The use of granulocyte colony-stimulating factor was accepted only if adverse hematologic toxic effects recurred despite an initial dose reduction.

A substitution of carboplatin for cisplatin was allowed only under the following circumstances: severe renal toxicity (defined as a measured creatinine clearance <45 mL/minute per 1.73 m^2) or substantial hearing loss and/or WHO grade 3 or 4 neurotoxicity. In the latter case (i.e., WHO grade 3 or 4 neurotoxicity), paclitaxel was also discontinued. Additional reasons for premature discontinuation of paclitaxel included severe hypersensitivity reactions and severe cardiac arrhythmias.

Finally, in patients without disease progression, chemotherapy options permitted beyond six cycles included: in the CP arm—CP, cyclophosphamide–carboplatin, cyclophosphamide alone, cisplatin alone, and carboplatin alone; in the TP arm—TP, paclitaxel–carboplatin, paclitaxel alone, cisplatin alone, carboplatin alone, and carboplatin and cyclophosphamide.

Quality Assurance

The study was conducted according to the quality-assurance standard operating procedures of each of the four cooperative groups. Seven EORTC centers (Monza, Leuven, Antwerp, Roma, Aviano, Rotterdam, and Brussels) were visited by a medical oncologist (J.-A. Roy), who reviewed the 129 patient charts for a number of important study aspects, including patient informed consent, patient eligibility, protocol compliance, clinical and/or surgical response, and documentation of progressive disease.

The data collected by each group were reviewed by the respective study group chairman, with particular attention paid to the pathology reports, the surgical reports, and the documentation of response and progression status. To ensure homogeneity in this review process, a study chairman evaluation form was designed and filled in for each patient entered in the trial. This form gave all the essential information on patient eligibility, reasons for noneligibility, tumor histology and tumor grade, status after initial surgery, disease measurability at entry, best clinical response, surgical response at the time of interval debulking surgery, if any, or the time of second-look surgery, if any, reason for protocol treatment discontinuation, and assessment of progression. Of note, one study chairman (M. J. Piccart), without knowledge of the randomization arm, reviewed all of the study chairman evaluation forms and clarified unclear items with the other three study coordinators. This “validated” information prevailed in the case of discordance with original case report forms and was entered into the database.

Definition of Study End Points

PFS, the primary study end point, was defined as the interval between the date of randomization and the date of progression of the disease or death or start of a new therapy without evidence of progression, whichever occurred first. Other study end points included clinical response rate, overall survival, quality of life, cost-effectiveness, and the potential use of CA 125 as a surrogate for patient outcome. Overall survival was defined as the interval between the date of randomization and the date of death. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor, including normalization of CA 125 level, determined by two observations not less than 4 weeks apart. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of the measured lesions, determined by two observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of new lesions was permitted. Nonmeasurable lesions had to remain stable or regress for inclusion in this category. Stable disease was defined as a steady state of response less than a PR or progression less than 25% lasting at least 4 weeks. No new lesions were to appear for inclusion in this category. Progressive disease (PD) was defined as the unequivocal increase of at least 25% in the sum of the products of the perpendicular diameters of the measured lesions. Appearance of new lesions also constituted PD; this definition of progression differs from the WHO definition in the use of the sum of the products of individual lesions. Of note, a rise in CA 125 alone was not considered to be PD. In view of the relatively small proportion of patients who underwent secondary surgical interventions in the two arms, the best clinical response was defined regardless of these surgical procedures, which were part of a predefined center policy.

Statistical Analyses

It was calculated that a total of 600 assessable patients would permit the detection of a 33% improvement in the median PFS of patients in the standard

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Table 1. Guidelines for administration of cyclophosphamide–cisplatin and paclitaxel–cisplatin regimens to patients with ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide + cisplatin</th>
<th>Paclitaxel + cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premedication</strong></td>
<td>None</td>
<td>Dexamethasone, 20 mg orally, 12 h and 6 h before paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diphenhydramine, 50 mg intravenously, 30 min before paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranitidine, 50 mg intravenously, 30 min before paclitaxel</td>
</tr>
<tr>
<td><strong>Prehydration</strong></td>
<td>1 L of NaCl (0.9%) in 3 h</td>
<td>1 L of NaCl (0.9%) for 3 h</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td>Yes, together with 500 mL of NaCl (0.9%) for 0.5–1 h</td>
<td>Yes, together with 500 mL of NaCl (0.9%) for 0.5–1 h</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Rapid infusion or injection (&gt;5-min administration)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td>In 500 mL of NaCl (0.9%)/glucose (5%) (2:1) containing 30 g of mannitol, 10 mEq of KCl, and 2 g of MgSO_4 for 1 h</td>
<td>In 500 mL of NaCl (0.9%)/glucose (5%) (2:1) containing 30 g of mannitol, 10 mEq of KCl, and 2 g of MgSO_4 for 1 h</td>
</tr>
<tr>
<td><strong>Posthydration</strong></td>
<td>1 L of NaCl (0.9%)/glucose (5%) (2:1) for 3 h for outpatients</td>
<td>1 L of NaCl (0.9%)/glucose (5%) (2:1) for 3 h for outpatients</td>
</tr>
<tr>
<td></td>
<td>2–3 L of NaCl (0.9%)/glucose (5%) (2:1) for 15 h for inpatients</td>
<td>2–3 L of NaCl (0.9%)/glucose (5%) (2:1) for 15 h for inpatients</td>
</tr>
<tr>
<td><strong>For outpatients discharge only if</strong></td>
<td>Minimal nausea and vomiting</td>
<td>Same as the previous column plus lack of hemodynamic disturbances and hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>Ability to take fluids orally</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output ≥250 mL/h</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Whole duration of treatment, h</th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.5–8</td>
<td>7.5–8</td>
</tr>
<tr>
<td></td>
<td>22.5–23</td>
<td>22.5–23</td>
</tr>
</tbody>
</table>
arm at a two-sided significance level of 5% and with a power of 80%. These calculations were based on an accrual time of 18 months, followed by 24 months after the trial was closed to patient entry. No interim analysis was planned.

The analyses of PFS and overall survival were based on the intent-to-treat policy. (All randomly assigned patients were analyzed according to the arm to which they were assigned.) The survival curves were estimated with the help of the Kaplan–Meier technique (3). Differences in the time-to-event end points were compared with the use of a two-sided stratified log-rank test (4). To adjust for confounding covariates, we also estimated the treatment effect by Cox’s proportional hazards regression model (5) and checked the proportional hazards assumptions (6). The analysis of response to treatment was restricted to the eligible patients with measurable disease at entry (unidimensional and/or bidimensional measures), assessed as such by the study coordinators of the groups (evaluation form).

Safety analysis was restricted to the patients who started treatment according to the protocol and for whom at least one cycle of chemotherapy had been documented. Comparisons of the rates of grade 3 or 4 toxicity were carried out. Comparisons of proportions between the two arms were done by use of a two-sided chi-squared test or a two-sided Fisher’s exact test if the number of patients in a given category was five or fewer (7). The two-sided Kruskal–Wallis test was used to compare the treatment effects of continuous variables (8).

The percentages given in the tables are exact; those in the text are rounded for clarity.

### Participating Institutions

A total of 73 institutions participated in the study; 27 belonged to the EORTC, 16 to the NOCOVA, 22 to the NCI-C-CTG, and eight to the Scottish Groups. The “Appendix” section gives a complete list of the participating centers and the principal investigators.

### RESULTS

#### Characteristics of Patients

Six hundred eighty women with epithelial ovarian cancer entered the trial. Twelve were ineligible: Six had cancer but did not have ovarian cancer, four had a second malignancy, one had an inappropriate stage of cancer, and one was in poor medical condition. The eligible patients were randomly assigned to one of two groups receiving the CP combination regimen (n = 338) or the TP combination regimen (n = 342). For the CP regimen, 336 patients started treatment; of those 336, a total of 330 were fully eligible. For the TP regimen, 339 started the treatment, and 336 patients started treatment; of those 336, a total of 330 were fully eligible. As shown in Table 2, both groups were well balanced for age, WHO performance status, FIGO stage, and amount of residual disease following staging laparotomy, presence of measurable disease, cell type, and tumor grade. Of note, less than 10% of the patient population had FIGO stage IIB or IIC disease, and roughly one third had optimal residual disease.

#### Chemotherapy Administration

Details of drug delivery are given in Table 3. A median number of six courses (cycles), with a range from 0 to 10, was given to each treatment group. Almost similar proportions of patients in each arm continued treatment beyond cycle 6: 26% in the CP group and 33% in the TP group; 18.5% in the CP group and 23.5% in the TP group received up to nine cycles of treatment. Of the 675 patients who started the treatment protocol, a low proportion of patients, amounting to 12% in the TP arm and 9% in the CP arm, had cisplatin replaced by carboplatin during the course of their chemotherapy.

Escalation of the paclitaxel dose to 200 mg/m², as recommended by the protocol, was done in 71% of the patients who did not experience profound myelosuppression following their first course at 175 mg/m². The median cumulative dose of paclitaxel given and its median dose intensity achieved (with their 25th and 75th percentiles) were 1173 (1051 and 1531) mg/m² and 59 (55 and 64) mg/m² per week, respectively.

Cisplatin administration was analyzed carefully in both groups. While no difference emerged between the total delivered dose of cisplatin, with an identical median cumulative dose of 450 mg/m² and similar 25th and 75th percentiles of the actual dose delivered, the median cisplatin dose intensity achieved was higher in the TP arm than in the CP arm: 24.4 versus 22.4 mg/m² per week. This difference, which was statistically significant, could be explained by a lower proportion of paclitaxel-treated patients experiencing at least one cycle with cisplatin dose delay: 36% compared with 60% (P = .001). Table 3 also shows that the protocol instructions not to diminish the cisplatin dose were not always followed. Here, however, more frequent cisplatin dose reductions or switch to carboplatin did occur in the TP arm.

#### Toxicity

Analysis of toxicity has been carried out in 675 patients who started their treatment and had at least one course documented for the occurrence of treatment-related side effects. The percentage of patients with grade 3 or 4 adverse effects (Common Toxicity Criteria, National Cancer Institute, Bethesda, MD) is displayed in Table 4 according to treatment group; to facilitate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cyclophosphamide + cisplatin (n = 338)</th>
<th>Paclitaxel + cisplatin (n = 342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>58 (22–85)</td>
<td>58 (23–79)</td>
</tr>
<tr>
<td>WHO performance status, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>171 (50.6)</td>
<td>159 (46.5)</td>
</tr>
<tr>
<td>1</td>
<td>125 (37.0)</td>
<td>138 (40.4)</td>
</tr>
<tr>
<td>2</td>
<td>40 (11.8)</td>
<td>40 (11.7)</td>
</tr>
<tr>
<td>3 or missing</td>
<td>2 (0.6)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>FIGO stage, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB or IIC</td>
<td>23 (6.8)</td>
<td>22 (6.4)</td>
</tr>
<tr>
<td>III</td>
<td>245 (72.5)</td>
<td>256 (74.9)</td>
</tr>
<tr>
<td>IV</td>
<td>70 (20.7)</td>
<td>64 (18.7)</td>
</tr>
<tr>
<td>Amount of residual disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or microscopic</td>
<td>53 (15.7)</td>
<td>60 (17.5)</td>
</tr>
<tr>
<td>Macroscopic, ≤1 cm</td>
<td>63 (18.6)</td>
<td>72 (21.1)</td>
</tr>
<tr>
<td>Macroscopic, &gt;1 cm</td>
<td>221 (65.4)</td>
<td>209 (61.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Measurable disease, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>161 (47.6)</td>
<td>162 (47.4)</td>
</tr>
<tr>
<td>No</td>
<td>176 (52.1)</td>
<td>180 (52.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cell type, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td>212 (62.7)</td>
<td>235 (68.7)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>46 (13.6)</td>
<td>31 (9.1)</td>
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<tr>
<td>Mucinous adenocarcinoma</td>
<td>18 (5.3)</td>
<td>12 (3.5)</td>
</tr>
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<td>Clear-cell adenocarcinoma</td>
<td>18 (5.3)</td>
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<tr>
<td>Other</td>
<td>44 (13.0)</td>
<td>49 (14.3)</td>
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<tr>
<td>Tumor grade, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: well differentiated</td>
<td>29 (8.6)</td>
<td>28 (8.2)</td>
</tr>
<tr>
<td>2: moderately well differentiated</td>
<td>86 (25.4)</td>
<td>92 (26.9)</td>
</tr>
<tr>
<td>3: poorly differentiated</td>
<td>192 (56.8)</td>
<td>197 (57.6)</td>
</tr>
<tr>
<td>Missing, not applicable</td>
<td>31 (9.2)</td>
<td>25 (7.3)</td>
</tr>
</tbody>
</table>


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comparisons with the GOG study #111, the analysis has been done both for the first six cycles and for all cycles of therapy.

As expected, substantially more patients in the TP group experienced severe myalgia, neurosensory and neuromotor symptoms, alopecia, and hypersensitivity reactions. In contrast, grade 3 or 4 vomiting was considerably more frequent in the CP group. It is interesting that, in this trial in which a 3-hour paclitaxel infusion time was used, febrile neutropenia (defined as fever $\geq 38^\circ C$ with a neutrophil count of $<0.5 \times 10^9/L$) was rare and occurred only in 3% of the patients, with no difference between the two treatment groups. Grade 3 or 4 toxicity rates for white blood cell counts, granulocyte counts, platelet counts, and hemoglobin levels were much lower in the CP arm than in the TP arm. Of note, infection, stomatitis, and ototoxicity were each encountered in fewer than 5% of the patients; a rise in the creatinine level above the upper normal limit (grade 1 or grade 2) was also a relatively infrequent event: 10% in the CP arm and 13% in the TP arm. The general acceptance of the two regimens

Table 4. Treatment delivery to patients with ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide + cisplatin (n = 336)</th>
<th>Paclitaxel + cisplatin (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median No. of cycles per patient (range)</strong>*</td>
<td>6 (0–10)</td>
<td>6 (0–10)</td>
</tr>
<tr>
<td><strong>No. (%) of patients who received &gt;6 cycles of therapy</strong></td>
<td>88 (26.2)</td>
<td>113 (33.3)</td>
</tr>
<tr>
<td><strong>No. (%) of patients with a switch to carboplatin</strong></td>
<td>30 (8.9)</td>
<td>40 (11.8)</td>
</tr>
<tr>
<td><strong>No. (%) of patients with paclitaxel dose escalation</strong></td>
<td>— (——)</td>
<td>241 (71.1)</td>
</tr>
<tr>
<td><strong>No. (%) of patients with cisplatin dose escalation</strong></td>
<td>— (——)</td>
<td>241 (71.1)</td>
</tr>
<tr>
<td><strong>Dose reduction†</strong></td>
<td>72 (21.4)</td>
<td>102 (30.1)</td>
</tr>
<tr>
<td><strong>Dose delay</strong></td>
<td>201 (59.8)</td>
<td>123 (36.3)</td>
</tr>
<tr>
<td><strong>Median cisplatin dose intensity, mg/m² per wk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Theoretical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>22.4</td>
<td>24.4</td>
</tr>
<tr>
<td><strong>Achieved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>450</td>
<td>450</td>
</tr>
<tr>
<td></td>
<td>(420–465)</td>
<td>(382–488)</td>
</tr>
<tr>
<td><strong>No. (%) of patients receiving 90% of theoretical cisplatin dose</strong></td>
<td>165 (49.1)</td>
<td>254 (74.9)</td>
</tr>
</tbody>
</table>

*This information pertains to the entire patient population (n = 680), while the rest of the table pertains to patients who received at least one cycle of therapy (n = 675). A few patients in each group never started treatment (0 cycle).

†Includes also a substitution of cisplatin by carboplatin at any time or no drug given.

‡P<.001 (chi-squared test).

§P<.001 (Kruskal–Wallis test).

Table 4. Adverse effects per treatment group analyzed for six cycles or all cycles in 675 assessable patients with ovarian cancer: NCI-CTC scale, worst grade per patient*

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide + cisplatin (n = 336)</th>
<th>Paclitaxel + cisplatin (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>104 (31)</td>
<td>103 (31)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>135 (40)</td>
<td>141 (42)</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>9 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (1)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>15 (4)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (1)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>60 (18)</td>
<td>65 (19)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>51 (15)</td>
<td>54 (16)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>7 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Stomatitis, grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>66 (20)</td>
<td>72 (21)</td>
</tr>
<tr>
<td><strong>Alopecia, grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Neurovascular symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (0.6)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Myalgia, grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>14 (4)</td>
<td>14 (4)</td>
</tr>
<tr>
<td><strong>Severe hypersensitivity reactions†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*NCI-CTC = National Cancer Institute Common Toxicity Criteria. All percentages are rounded.

†Hypersensitivity reactions resulted in one or more of the following: hypotension or respiratory distress requiring therapy, angioedema, and generalized urticaria.
was reflected by the low proportion of patients prematurely dis-
continuing treatment for toxicity (defined as fewer than six
cycles): 4.5% in the CP arm and 6.5% in the TP arm.

Clinical Response

Clinical response could be assessed in 323 patients who en-
tered the study with clinically or radiologically measurable dis-
ease. The overall response rate was 58% in the TP group and
45% in the CP group; the complete clinical remission rates were
41% and 27%, respectively; both differences were statistically
significant (both $P$ values = .01, chi-squared test) (Table 5).
Imaging techniques, which are expensive and sometimes un-
pleasant, were not always repeated to confirm the response.
When these unconfirmed responses were also taken into ac-
count, the global response rate was 78% in the TP arm and
remained superior to the 67% response rate observed in the CP
arm.

Surgical Interventions After Randomization

The proportion of patients who underwent surgical interven-
tions after randomization was low in the two treatment groups:
Interval debulking surgery was performed in 7% of the patients
assigned to the CP arm and in 8% of the patients assigned to the
TP arm; the corresponding values for second-look surgery were
20% and 25%, respectively. Only 154 patients underwent a sec-
ond-look procedure: 68 patients in the CP group and 86 patients
in the TP group. The rates of pathologically documented com-
plete remissions were 25% and 42.5%, respectively; the corre-
sponding values for microscopic residual disease were 20.5% and
23%, respectively. Since surgical response evaluation was not
integrated into the treatment plan, these two subgroups of
patients cannot be compared.

Crossover to the Paclitaxel Regimen at First Progression of Disease in the Cyclophosphamide (Control) Arm

Table 6 shows that roughly half of the patients (48%) in the
CP arm were treated with paclitaxel at first progression of dis-
ease. This crossover rate was quite similar in groups of patients
treated in Europe and in Canada.

PFS and Overall Survival

At the time of submission of this article and with a median
follow-up of 38.5 months, 74% of the patients have shown pro-
gression of disease and 59% have died. Fig. 2 and Fig. 3, A,
show the progression-free and overall survival curves, respec-
tively, for all patients entered in the trial. Both PFS and overall
survival were statistically significantly longer for the patients in
the TP group. The median PFS was 15.5 months for patients in
the TP group and 11.5 months for patients in the CP group
(log-rank $P$ = .0005). An approximately 10-month difference in
median overall survival was particularly substantial in favor of
the TP arm (log-rank $P$ = .0016; median of 35.6 months for the
TP group versus 25.8 months for the CP group). A total of 34
patients, 14 in the CP group and 20 in the TP group, received
second-line therapy before disease progression was documented.
Censoring these patients at the time of this therapy in the PFS
analysis did not change the results.

A Cox regression analysis was performed to adjust the treat-
ment comparison for the known prognostic factors. When age,
performance status, FIGO stage, histologic type, histologic
grade, disease measurability, and residual disease were taken
into account, it appeared that the 26% reduction in the instan-
taneous rate of death (hazard ratio [HR] = 0.74; 95% confidence
interval [CI] = 0.63–0.88) and the 27% reduction in the instantan-
eous rate of progression (HR = 0.73; 95% CI = 0.60–
0.89), associated with the paclitaxel–cisplatin treatment, re-
mained qualitatively unchanged.

Although the trial did not have the power to compare the
chemotherapy regimens in the subsets of patients having optimal
or suboptimal residual disease, it is noteworthy that the treat-
ment effect goes in the same direction in these two groups of
patients (Fig. 3, B).

Table 5. Best clinical response in ovarian cancer patients receiving cyclophosphamide + cisplatin or paclitaxel + cisplatin treatments*

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide + cisplatin (n = 161)</th>
<th>Paclitaxel + cisplatin (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>44 (27.3)‡</td>
<td>66 (40.7)‡</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>28 (17.4)‡</td>
<td>29 (17.9)‡</td>
</tr>
<tr>
<td>CR unconfirmed</td>
<td>16 (9.9)</td>
<td>15 (9.3)</td>
</tr>
<tr>
<td>PR unconfirmed</td>
<td>19 (11.8)</td>
<td>16 (9.9)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>25 (15.5)</td>
<td>19 (11.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>21 (13.0)</td>
<td>8 (4.9)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.0)</td>
<td>9 (5.6)</td>
</tr>
</tbody>
</table>

*Only a subset of the clinical trial population had clinically measurable disease.
‡$P$ = .01 (chi-squared test).
§$P$ = .01 (chi-squared test); number indicates total percent of patients with complete response and partial response.

Table 6. Crossover of ovarian cancer patients to a taxane or taxane-based regimen from the cyclophosphamide + cisplatin arm

<table>
<thead>
<tr>
<th>Group†</th>
<th>Total No. of patients randomly assigned</th>
<th>No. of patients randomly assigned to CP‡</th>
<th>No. of patients whose disease progressed and/or who started a new therapy§ in the CP‡ arm</th>
<th>No. of patients who received a taxane§ in the CP‡ arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>231</td>
<td>115</td>
<td>94</td>
<td>50</td>
</tr>
<tr>
<td>NOCOVA</td>
<td>208</td>
<td>104</td>
<td>85</td>
<td>41</td>
</tr>
<tr>
<td>NCI-C-CTG</td>
<td>160</td>
<td>79</td>
<td>69</td>
<td>33</td>
</tr>
<tr>
<td>Scottish</td>
<td>81</td>
<td>40</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>680</td>
<td>338</td>
<td>277</td>
<td>132 (48%)</td>
</tr>
</tbody>
</table>

†EORTC = European Organization for Research and Treatment of Cancer; NOCOVA = Nordic Gynecological Cancer Study Group; NCI-C-CTG = National Cancer Institute of Canada Clinical Trials Group; Scottish = Scottish Group.
‡CP = cyclophosphamide–cisplatin.
§Two hundred sixty-three patients received this new therapy because of disease progression and 14 received it without evidence of progression.
§§Paclitaxel was the only taxane given.
In view of the wider availability of paclitaxel at the time that the European–Canadian intergroup trial was conducted, a higher crossover rate to paclitaxel than in the GOG #111 study was expected to occur in the cyclophosphamide or the “control” arm. Therefore, PFS was selected as the primary trial end point, with the implementation of a strict patient follow-up policy prohibiting second-line treatment before documented progression.

Other end points included overall survival, clinical response, and qualitative and quantitative evaluations of toxic effects associated with each regimen, as were studied in the GOG #111 study. Also evaluated were quality of life, cost-effectiveness, and the possibility of CA 125 being a surrogate for patient outcome. Observations made in relation to these three latter end points will form the subject of separate reports.

Other differences between our study and the GOG #111 study included broader criteria for patient selection in our study with...
the additional recruitment of patients with optimally debulked stage III or IV disease as well as patients having FIGO stage IIB or IIC disease and a flexible center policy concerning secondary surgical interventions as opposed to the integration of second-
look laparotomy in the treatment plan of the GOG study. A
further difference from the GOG #111 study was the intro-
duction in our study of interval debulking surgery as an option in
view of the survival advantage associated with this procedure in
a randomized clinical trial previously published by the Gyneco-
logical Cancer Cooperative Group of the EORTC (9). Last, but
not least, chemotherapy administration differed between our
study and the GOG #11 trial. In contrast to a fixed number of six
cycles of cisplatin-based therapy in the GOG #111 trial, up to
nine cycles were allowed in our study, as well as a replacement
of cisplatin by carboplatin in the cases of substantial neurotox-
icity or nephrotoxicity; moreover, a higher paclitaxel dose per
cycle of 175 mg/m² (with a possible escalation to 200 mg/m²),
a higher cumulative dose, and a shorter paclitaxel infusion time
of 3 hours instead of 24 hours were used in our study. The
rationale for these modifications was twofold: 1) the desire to be
as close as possible to common practice and 2) the hope that the
new paclitaxel schedule would be more convenient and perhaps
less toxic than the one used by the GOG. Indeed, paclitaxel
infused over a 3-hour period had been shown in a previous
European–Canadian collaborative trial to be effective in the
treatment of relapsed disease and to produce less neutropenia
than paclitaxel given over a 24-hour period (10); moreover, the
3-hour strategy would allow the administration of a higher pa-
clitaxel dose, exploiting potential dose–response effects
suggested by the results of the previously mentioned study.
The previous European–Canadian trial, indeed, used a 2 × 2
factorial design for the paclitaxel dose (135 or 175 mg/m²) and
the paclitaxel infusion time (24 hours or 3 hours) and found a
PFS advantage for the 175-mg/m² dose and the 3-hour infusion
(10).

The mature results of the present European–Canadian inter-
group trial for women with advanced ovarian cancer confirm the
findings of the GOG #11 trial published in 1996 (2) that the
combination of cisplatin and paclitaxel confers a survival ad-
vantage over the combination of cyclophosphamide and cisplat-
in. Importantly, they also extend these findings in that the trial
included a broader range of patients, was conducted in a largely
community-based setting, and included a much higher rate of
crossover to paclitaxel on first progression of disease in the
standard arm: 48% in our study instead of 8% in the GOG study.
The fact that the 3-year survival results of this intergroup trial
mirror those of the GOG #111 trial has two important impli-
cations: 1) It provides strong or level 1 evidence that the paclitax-
el–cisplatin regimen is superior to the cyclophosphamide–
cisplatin regimen, a widely accepted standard of care for patients
with advanced ovarian cancer prior to the taxane era and, there-
fore, it establishes this regimen as the gold standard for this
disease; and 2) it refutes the claim that administration of pacli-
taxel should be delayed until relapse.

This latter conclusion does not contradict the findings of
another GOG trial, GOG #132, which compared single-agent
cisplatin, single-agent paclitaxel, and a combination of cisplatin
and paclitaxel (11). In that study, no survival advantage emerged
for the combination, but a high rate of early crossover (before
disease progression) from cisplatin to paclitaxel and from pacli-
taxel to cisplatin occurred in the two single-agent arms, which
likely blurred the differences in overall survival among the three
groups.

The medical oncology community has rarely been gratified in
the last two decades as it has been with these two consecutive
randomized clinical trials—the GOG #111 trial and the Europe-
an–Canadian intergroup trial—addressing a similar question
and showing so many similarities in outcomes, yet some concerns
have still been raised (chiefly those related to the appropriateness
of the control arm). It has been suggested that “CP” is a
suboptimal reference treatment on the basis of the ICON2 (In-
ternational Collaborative Ovarian Neoplasm) trial showing
equivalence between CAP (i.e., a combination of cyclophospha-
mide, doxorubicin, and cisplatin) and single-agent carboplatin
and on the basis of a meta-analysis showing superiority of CAP
over CP (12, 13).

We have recently given our point of view on the risks of
comparing results from different trials (14), and we think that
meta-analyses of randomized trials in ovarian cancer are blunted
by the poor quality of trials that they aim to review. The pre-
liminary results of ICON3, a very large trial comparing carbo-
platin or CAP with carboplatin–paclitaxel, are provocative (15),
with no apparent overall advantage to the paclitaxel combination
arm. However, the follow-up is only 18 months and is much too
short in comparison to the GOG #11 trial or the European–
Canadian intergroup trial to make meaningful conclusions at this
stage.

We probably failed to improve the therapeutic index of the
paclitaxel–cisplatin combination by reducing the infusion
duration of paclitaxel: Our 14% rate of grade 3 neurotoxicity
during six treatment cycles seems to be higher than the 4%
rate recorded in the GOG #111 trial; also, both the escalation of
the paclitaxel dose from 175 to 200 mg/m² (built into the
protocol at a time when many uncertainties persisted regarding
the optimal dose and schedule of paclitaxel in ovarian cancer)
and the permission to give nine cycles of therapy (in the event
that the investigator thought that previous randomized evidence
favoring six cycles was not necessarily applicable to a new
regimen) have contributed to the high incidence of neurotoxicity
observed in our trial. Moreover, efficacy data do not
suggest any hints of superiority. Indeed, despite the inclusion of
a more favorable group of patients in our trial, the median
survival was increased by 10 months in our trial instead of
14 months in the GOG #111 trial. A plausible explanation
for this reduced impact of paclitaxel might be the more frequent
and earlier crossover to paclitaxel in the control arm of our
study.

Nevertheless, a panel of experts (16) recently recommended
the GOG #111 regimen rather than the intergroup regimen when
the combination of paclitaxel and cisplatin is used. It is likely,
however, that the GOG #111 regimen will soon be supplanted by
the carboplatin–paclitaxel combination. Three randomized trials
of carboplatin–paclitaxel versus cisplatin–paclitaxel have been
conducted, with the aim of showing greater ease in treatment
administration, reduced toxicity, and no loss in efficacy for the
carboplatin-based regimen. These trials have recently been well
reviewed (17); this review concluded that at least the first two
goals have been reached, while preliminary data on efficacy
from the two European trials so far do not indicate any trend of
inferiority for the carboplatin–paclitaxel combination. Results of
the third trial, conducted in optimally debulked tumors in the
United States, have been reported at the 1999 meeting of the

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American Society of Clinical Oncology and, indeed, indicate similar efficacy (18). It will also be interesting to see how a docetaxel–carboplatin regimen compares with the paclitaxel–carboplatin regimen. This question is currently being examined by the Scottish Group.

The European–Canadian intergroup trial represents a turning point in the history of the conduct of ovarian cancer trials. To our knowledge, it is the first trans-Atlantic intergroup trial that has successfully accrued 680 patients in only 15 months. It provided a learning curve for conducting intergroup trials, and, together with the ICON collaboration, it is the symbol of a profound mutation that has recently taken place in ovarian cancer clinical research (19). Let us hope that this change will be durable and will allow for the fast and coherent investigation of many other new active compounds, which carry the potential to further improve upon the results achieved with a taxane–platinum regimen in the treatment of advanced epithelial ovarian cancer.

APPENDIX: ALPHABETICAL LISTING OF PRINCIPAL INVESTIGATORS, STATISTICIANS, AND CLINICAL MONITORS OF THE INTERGROUP CLINICAL TRIAL FOR PATIENTS WITH ADVANCED OVARIAN CANCER

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NOTES

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