A Phase I Study of Continuous Infusion Doxorubicin and Paclitaxel Chemotherapy with Granulocyte Colony-Stimulating Factor for Relapsed Epithelial Ovarian Cancer


Vincent Gynecology, Division of Gynecologic Oncology [L. R. D., A. G., A. F. F., N. N.], Division of Hematology and Oncology [R. P., J. G. S., T. M., M. V. S.], and Division of Biostatistics [D. M. F.], Massachusetts General Hospital [J. G., K. B.], Boston, Massachusetts 02114

ABSTRACT

A Phase I study of paclitaxel and doxorubicin administered as concurrent 96-h continuous i.v. infusion was performed to determine the maximum tolerated dose (MTD), principal toxicities, and pharmacokinetics of this combination in women with relapsed epithelial ovarian cancer. The paclitaxel dose was fixed at 100 mg/m² (25 mg/m²/day for 4 days). The dose of doxorubicin was escalated from 30 mg/m² (7.5 mg/m²/day for 4 days) in increments of 10 mg/m² until dose-limiting toxicity was observed. All patients received granulocyte colony-stimulating factor 5 μg/kg/day prophylactically. Apparent steady-state plasma levels of both drugs were determined in the final cohort of patients treated at the MTD. A total of 17 patients received 52 cycles of therapy. The median age was 58 years, and all patients had previously received one to five different regimens (median, 2) of chemotherapy, including both platinum and paclitaxel. The treatment was tolerated well, with grade 1–2 nausea being the most frequent side effect (73% of cycles). Anemia, neutropenia, thrombocytopenia, and mucositis became dose limiting at the fourth dose level, defining the MTD of doxorubicin in this regimen as 50 mg/m². There were four partial responses and one complete response in 15 evaluable patients. Apparent steady-state plasma concentrations (mean ± SD) of paclitaxel and doxorubicin in the three patients treated at the MTD were 33.9 ± 12.5 nM and 15.7 ± 1.3 nM, respectively. Paclitaxel and doxorubicin by continuous infusion is a well-tolerated and active chemotherapy regimen for recurrent ovarian cancer.

INTRODUCTION

Ovarian carcinoma is the most lethal gynecological malignancy in the United States. Although initial response rates to platinum-based chemotherapy are high, 80% of patients will present with relapsed disease and require further treatment (1). Patients with progressive disease after treatment with combination paclitaxel and platinum chemotherapy have particularly dismal response rates to additional chemotherapy. Modest activity, typically in the range of 15–30%, has been described for carboplatin, topotecan, etoposide, ifosfamide, and liposomal doxorubicin (2–7). More effective agents or combinations are needed.

Preliminary data have been reported demonstrating clinical responses in breast cancer patients with the use of 96-h continuous i.v. infusion paclitaxel in women who have progressive disease after shorter duration infusion taxane therapy (8, 9). Moreover, there has been considerable interest in evaluating the combination of doxorubicin and paclitaxel as salvage therapy for women with metastatic breast cancer. The regimen of doxorubicin, 60 mg/m², given before the paclitaxel dose of 150–250 mg/m² over 3 or 24 h is highly efficacious in women with metastatic breast cancer, demonstrating up to a 90% response rate with up to a 40% complete response rate in some small studies (10, 11). These reports suggest that this combination might also be successful in patients with recurrent ovarian cancer treated previously with taxane-based therapy, especially because doxorubicin has already proven to be clinically effective against metastatic ovarian cancer, with a single-agent response rate of ~30% (12).

Typical toxicities encountered with the combination of paclitaxel and doxorubicin include dose-limiting mucositis and neutropenia. The administration of single-agent paclitaxel chemotherapy, given i.v. at a daily dose of 35 mg/m² for 4 days, was complicated by neutropenia in 63% of patients but was otherwise well tolerated with an ~10% incidence of grade 3 thrombocytopenia, anemia, stomatitis, nausea, and neuropathy (8, 9). In addition, there has been a moderately high incidence of cardiac toxicity, especially at higher doses of doxorubicin (13), suggesting the possibility that paclitaxel therapy may enhance the cardiotoxicity of doxorubicin. In comparison to bolus i.v. doxorubicin, longer infusions have been shown to significantly decrease the incidence of the cardiotoxic effects. In a randomized study of 15–30 min doxorubicin versus 6 h doxorubicin in...
patients with breast and ovarian carcinoma, short infusion therapy had a 14% incidence of congestive failure, whereas no cardiotoxicity was observed with a 6-h infusion (14). Longer infusions of doxorubicin seem equally efficacious as short infusions, with less nausea and vomiting but more mucosal toxicity (15, 16).

A Phase I study was therefore designed to examine the combination of doxorubicin with paclitaxel chemotherapy as a 96-h, concurrent, continuous infusion with women with recurrent ovarian carcinoma, all of whom had received platinum and taxane-based therapy previously. The primary aim of the study was to define the toxicity of the therapy and to determine the MTD\(^3\) of doxorubicin in this regimen. Secondary goals were to begin to evaluate potential efficiency of this schedule and combination in a population of women with recurrent ovarian cancer.

**MATERIALS AND METHODS**

Women with histopathologically confirmed epithelial ovarian carcinoma and documented recurrent disease defined as new ascites with positive cytology, biopsy-proven relapse, or a rising CA-125 more than 1 month since previous treatment were eligible for this study. Other eligibility criteria included a prior platinum-containing chemotherapy, a GOG performance status ≤2, and a cardiac ejection fraction (LVEF) ≥45%. Patients were excluded if they had a history of congestive heart failure, active angina pectoris or myocardial infarction within 6 months of treatment, an electrocardiogram with significant ischemia or conduction defect, a serum creatinine >1.5 mg/dl, or serum bilirubin (direct) and aspartate aminotransferase >1.5 times the upper limit of the normal range. The protocol was approved by the Institutional Review Board, and each patient entered gave written informed consent. All toxicities were graded according to the GOG common toxicity criteria.

Both chemotherapy agents were administered as a 96-h continuous i.v. infusion that patients could receive in an outpatient or inpatient setting. All patients receiving outpatient therapy had a double lumen Hickman catheter placed prior to the initiation of chemotherapy. Patients receiving inpatient therapy required a single lumen central access device at a minimum. Paclitaxel (Taxol; Bristol Meyers Squibb) was given at a fixed dose of 25 mg/m\(^2\)/day for 4 days, beginning 1 h after initiating the doxorubicin infusion. The dose of doxorubicin (Ben Venue) was escalated in cohorts of three to five patients from 7.5 to 10 to 12.5 to 15 mg/m\(^2\)/day (Table 1). All doses were based on actual body weight as measured at the beginning of each cycle. Pretreatment prophylactic medications included dexamethasone, diphenhydramine, and perphenazine. G-CSF (Neupogen; Amgen) was administered at a dose of 5 \(\mu\)g/kg given s.c. daily beginning on day 6 and continuing until the absolute neutrophil count exceeded 10,000/µl. Treatment was repeated every 21 days if there was complete resolution of mucositis, a platelet count >100,000/µl, and a WBC count >3500/µl. A 1-week delay was permitted on the protocol.

The MTD was defined as the dose level below that in which two patients experienced DLT or grade 3 nonhematological or grade 4 hematological toxicity. Neutropenia was only considered a DLT if associated with fever. DLTs were determined only on cycle 1 of chemotherapy. Patients with grade 3 or 4 toxicity on later cycles had doses adjusted as detailed below (17).

Patients underwent gated blood pool scan before beginning therapy and again after completing three cycles. Patients with a drop in ejection fraction of >10% (but still >40% ejection fraction) could receive additional therapy but were to be followed with gated blood pool scan after each cycle. Patients with an ejection fraction dropping below 40% or experiencing an additional 5% reduction in ejection fraction were to be taken off study. In addition, patients with grade 3 nonhematological (excluding mucositis) or grade 4 hematological toxicities were taken off protocol. The doxorubicin dose was reduced by 15% for neutropenia with fever, grade 3 or 4 mucositis, or platelet nadir <50,000/mm\(^3\).

All patients had serum CA-125 measurements before each cycle. Radiological evaluations were repeated after three cycles and each three cycles thereafter. Patients continued on therapy until two cycles past clinical complete response or until evidence of progressive disease or a cumulative doxorubicin dose of 360 mg/m\(^2\). In patients with measurable disease, the following definitions were used (18): a CR was the complete disappearance of all clinical measurable disease and a CA-125 <35 units/liter for a minimum of 30 days after therapy; a PR was a >50% reduction in the sum of the bidimensional measurements of measurable disease for a minimum of 30 days and reduction in CA-125 of at least 50%; and progressive disease was a >25% increase in the sum of the bidimensional measurements of measurable disease for a minimum of 30 days and reduction in CA-125 of at least 50%; and progressive disease was a >25% increase in the sum of the bidimensional measurements of measurable disease, >25% increase in CA-125, or new disease sites on imaging. Stable disease was a less than PR without progressive disease for at least 3 weeks. For patients with nonmeasurable disease, a CR was defined as the normalization of CA-125 and complete resolution of pleural fluid and ascites if present. A PR was defined as the reduction in CA-125 by >50% with reduction in ascites or pleural effusion. In both categories of patients, a rising CA-125 without radiological or physical examination documentation was considered progressive disease.

Plasma concentrations of paclitaxel and doxorubicin achieved during the concurrent 96-h continuous i.v. infusions were determined during the first cycle of therapy in the final group of three patients treated at the MTD of the combination (100 mg/m\(^2\) paclitaxel and 50 mg/m\(^2\) doxorubicin), as well as a

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Table 1. Dose escalation scheme

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Paclitaxel</th>
<th>Doxorubicin</th>
<th>n</th>
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<tr>
<td>1</td>
<td>25 mg/m(^2)/day</td>
<td>7.5 mg/m(^2)/day</td>
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</tr>
<tr>
<td>4</td>
<td>25 mg/m(^2)/day</td>
<td>15.0 mg/m(^2)/day</td>
<td>4</td>
</tr>
</tbody>
</table>

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\(^3\) The abbreviations used are: MTD, maximum tolerated dose; GOG, Gynecological Oncology Group; G-CSF, granulocyte colony-stimulating factor; DLT, dose-limiting toxicity; CR, complete response; PR, partial response; CT, computed tomography; CV, coefficient of variation.
The lower limit of quantitation was 5.6 nM for paclitaxel were validated according to presently recommended criteria (20), with some minor modifications. The analytical methods were validated according to presently recommended criteria (21). The lower limit of quantitation was 5.6 nM for paclitaxel (interday CV, 11.7%) and 8.9 nM for doxorubicin (interday CV, 5.6%). Each plasma specimen was assayed in duplicate on separate days, together with a standard curve. The apparent steady-state concentration of drug achieved during the infusion ($C_{ss}$) was calculated as the geometric mean of the values for the five samples collected from each patient. Total body clearance ($CL$) was estimated according to the equation, $CL = \frac{R_0}{C_{ss}}$, where $R_0$ is the rate of drug infusion.

Duration of response was measured from the time of maximal response until disease progression. Progression-free interval was measured from the initiation of protocol chemotherapy until disease progression. Survival was measured from the time of initiation of protocol chemotherapy to death.

**RESULTS**

A total of 52 cycles of chemotherapy were given to 17 patients (median; 3; range, 1–6). A summary of clinical characteristics is given in Table 2. The median patient age at treatment was 58 years (range, 39–73), and the median performance status was 0. Fourteen patients had tumors of papillary serous histology, and 14 tumors were histological grade 3. Fifteen patients had measurable disease on entering the study, and the remaining two patients had an elevated CA-125 level only.

Table 2 also summarizes the previous chemotherapeutic treatments of the patients. The median number of prior courses of chemotherapy was two (range, 1–5). All patients had received both paclitaxel and a platinum compound during previous treatment. The median time since completing the last platinum treatment was 7 months (range, 1–19 months) and since completing the last paclitaxel treatment was 7 months (range, 1–27 months). Nine patients (53%) were platinum resistant, as defined by progression of disease during platinum therapy or progression of disease within 6 months of completing platinum therapy (1). Nine patients (53%) were taxane resistant, as defined by progression of disease during taxane therapy or progression of disease within 6 months of completing taxane therapy (1). Nine patients (53%) were taxane resistant using the criteria defined above. One patient had a history of treatment with whole abdominal radiation, and one patient had a history of palliative radiation therapy to her pelvis and back. Three patients had a history of treatment with peripheral blood stem cell-supported, high-dose carboplatin and cyclophosphamide chemotherapy.

Follow-up was available on all patients. The first 14 patients defined the MTD and DLT. An additional three patients were then enrolled at the MTD to better define the toxicity at this dose level and for pharmacological study. Four patients received only one course of therapy. One of these four patients was on dose level 2 and had a history of whole abdominal radiation therapy. She was taken off study for an increasing pelvic mass and bilateral hydrenephrosis. Two of the four patients were on dose level 3. One of these patients was taken off study for progressive disease, and the other was taken off study for prolonged pancytopenia. The fourth patient was on dose level 4 and was taken off study for prolonged myelosuppression and grade 3 mucositis. These four patients were included in the toxicity evaluation. Three of the four patients were included in the survival analysis (see below).

The major toxicities, both hematological and nonhematological, are summarized in Tables 3 and 4, respectively. Only toxicities for cycle 1 are detailed in the tables because cycle 1 was used to determine DLT. Over all cycles, four patients experienced grade 3–4 anemia, two had grade 3 mucositis, four had grade 3–4 leukopenia, and four had fever and neutropenia. In particular, for dose level 4 there were two cycles with grade 3 anemia, three cycles with grade 4 neutropenia, one cycle with grade 3 thrombocytopenia, and two cycles with grade 3 mucositis. There was no clinically significant cardiac toxicity during or after the trial in any of the patients. Two of seven patients who had two gated blood pool scans had a documented asymptomatic drop in left ventricular function.

Nonhematological toxicity (Table 4) was minimal and easily managed. Grades 1–2 nausea was experienced in 73% of cycles. Grades 1–2 nausea, fatigue, mucositis, and diarrhea were frequent but manageable. One patient experienced grade 3 diarrhea and 2 patients experienced grade 3 mucositis over all cycles. There were no treatment-related deaths.
At the maximum tolerated dose of 100 mg/m²/day paclitaxel and 50 mg/m² doxorubicin with G-CSF support, there was relatively little nonhematological toxicity. The treatment itself was successfully integrated into the ambulatory setting. Four of the six patients had been treated previously with either pelvic irradiation or high-dose chemotherapy. One patient who received prior pelvic irradiation suffered a decrease in performance status on treatment from 0 to 2, and one patient who had received high-dose chemotherapy to consolidate her second line treatment came off study with grade 4 neutropenia in the first cycle.

There were three line complications in two patients. One patient was admitted to the hospital with a right chest wall infection associated with her Hickman catheter and a Staphylococcus aureus bacteremia. This same patient had a central line discontinued during the following cycle secondary to erythema at the insertion site. One patient had her central line removed because of arm edema.

Only one patient required dose reduction. This patient was on dose level 4. She required a 15% dose reduction of doxorubicin for cycles two through six secondary to grade 4 neutropenia on cycle one.

Table 3  Hematological toxicities for cycle 1 by dose level

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Absolute neutrophil count</th>
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<th>Platelets</th>
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<td></td>
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<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
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<td>4</td>
<td>1 0 0 1 2</td>
<td>2 0 2 0 0</td>
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Table 4  Nonhematologic toxicities, cycle 1 only

<table>
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<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
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</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>Fatigue</td>
<td>Nausea</td>
<td>Mucositis</td>
</tr>
<tr>
<td>1</td>
<td>1 2 1 0 0</td>
<td>2 2 0 0 0</td>
<td>4 0 0 0 0</td>
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<table>
<thead>
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<th>Grade</th>
<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
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<td>Diarrhea</td>
<td>Vomiting</td>
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<td>4 0 0 0 0</td>
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Only one patient required dose reduction. This patient was on dose level 4. She required a 15% dose reduction of doxorubicin for cycles two through six secondary to grade 4 neutropenia on cycle one. Five patients required hospitalization for treatment-related toxicity, including one patient with a localized cutaneous herpes zoster infection requiring treatment with i.v. acyclovir, three patients with fever and neutropenia after cycle 1, and one patient with a right chest wall infection and bacteremia associated with a Hickman catheter.

Response to treatment is summarized in Table 5. Only 2 of 17 patients were considered to be nonevaluable for response. One of these received only one cycle of treatment on dose level 4 and was unable to tolerate any further treatment secondary to prolonged myelosuppression. The other patient had nonmeasurable disease by CT and had enlarged inguinal nodes that regressed during therapy. CA-125 was not informative. Because the nodes were not biopsied, she was considered evaluable for toxicity but not for response.

There was one CR and four PRs for a total response rate of 33% (95% confidence interval, 12–62%). The one patient with a CR was treated on dose level 4. She had two previous lines of chemotherapy, including peripheral stem cell-supported, high-dose cyclophosphamide and carboplatin. Her disease was defined as resistant to platinum or paclitaxel. The patient had resolution of CT-documented omental cake and subdiaphragmatic disease, as well as normalization of her CA-125. She remained free of disease for 3 months and continues to be alive with disease 23 months after protocol therapy. Among the four patients with PR, three had a reduction of their CA-125 levels to the mid 30s (39, 38, and 33), and two of these had a 50% reduction in diameter of measurable disease by CT scan. Two of these four patients had disease that was defined as both platinum and taxane resistant. Three of the patients with PR have since died of their disease; 7.4, 8.8, and 13.6 months after completion of protocol therapy. The remaining patient is alive with disease 32 months after treatment.

At the MTD, the mean (± SD) $C_{ss}$ of paclitaxel and doxorubicin were 33.9 ± 12.5 nM and 57.3 ± 4.8 nM, respectively. Plasma levels of doxorubicin tended to be more consistent than paclitaxel both within and between patients. In particu-
ular, the CV for plasma concentrations measured in individual patients during the infusion ranged from 10.4 to 24.1% for doxorubicin and 17.2 to 54.1% for paclitaxel. Similarly, the CV for the group mean $C_{\text{ss}}$ was 8.3% for doxorubicin, in comparison to 36.9% for paclitaxel. The corresponding $CL$ values (mean ± SD) were 37.3 ± 11.4 l/h/m² for paclitaxel and 57.3 l/h/m² for doxorubicin. Increasing the doxorubicin infusion rate to 15.0 mg/m²/day produced a proportionate increase in its $C_{\text{ss}}$ value, whereas the paclitaxel $C_{\text{ss}}$ was found to be lower than the 60–70 nm threshold concentration for severe toxicity in each of these patients, ranging from 26.0 to 49.5 nm. This very likely accounts for the acceptable neutropenia, as well as other paclitaxel-related toxicities in this trial, and suggests that G-CSF may not be necessary. In fact, G-CSF has proven to be ineffective in controlling granulocyte toxicity when the paclitaxel $C_{\text{ss}}$ afforded by the 96-h infusion schedule exceeds 70 nm.

The apparent $CL$ of paclitaxel observed in this study, 34.7 ± 10.7 l/h/m² (mean ± SD, $n = 4$) was very similar to values reported previously from studies of single-agent paclitaxel given as a 96-h infusion to breast cancer patients without metastatic liver involvement (8, 9). Therefore, paclitaxel pharmacokinetics is evidently not altered by the simultaneous administration of doxorubicin according to the same schedule. Likewise, the $CL$ of doxorubicin, 56.4 ± 4.4 l/h/m² ($n = 4$), was comparable with values determined in cancer patients treated with 48 and 72 h continuous i.v. infusions of the drug, either given alone or prior to other chemotherapeutic agents (10, 27). These findings are consistent with a report that the pharmacokinetic behavior of paclitaxel and doxorubicin were not affected when given by concurrent 72-h continuous i.v. infusions to patients with breast cancer (27).

In contrast, a clinically significant pharmacokinetic interaction between paclitaxel and doxorubicin was demonstrated in breast cancer patients during a trial to evaluate their administration by sequential 24-h and 48-h continuous i.v. infusions, respectively (10). Specifically, the $CL$ of doxorubicin decreased by 32% when the paclitaxel (125 mg/m²/24 h) infusion preceded doxorubicin (48 mg/m²/48 h) in comparison to the reverse sequence within the same cohort of patients. This resulted in a 70% higher mean doxorubicin plasma concentration at the end of infusion and a greater incidence of severe stomatitis. Both preclinical and clinical evidence suggests that the alteration in doxorubicin pharmacokinetics is directly attributable to Cremophor EL, used to solubilize paclitaxel (28, 29). Although the

**DISCUSSION**

The role of anthracyclines in the management of ovarian cancer has been debated over the last two decades. Conte et al. (22) reported a randomized trial comparing cisplatin plus cyclophosphamide (PC) versus cisplatin, doxorubicin, and cyclophosphamide in 125 patients with advanced ovarian cancer after primary surgery. Although the paper did not report a survival advantage for patients receiving anthracycline, the CR rate was 20% for cisplatin/cyclophosphamide and 40.6% for cisplatin/doxorubicin/cyclophosphamide ($P < 0.05$). This result was interpreted positively within Europe. However, this study was followed by a similar study with 349 evaluable patients from the GOG (23) in which there was no significant difference found in progression-free interval, frequency of negative second-look laparotomy, or survival for patients receiving anthracycline. Subsequently, a meta-analysis has suggested that the addition of doxorubicin to platinum-based chemotherapy in the prepaclitaxel era improves overall survival (24), with a similar degree of improvement to that reported with the addition of paclitaxel.

The combination of bolus doxorubicin and paclitaxel as a 3-h infusion is highly active in patients with metastatic breast cancer, but it can be associated with considerable cardiotoxicity (25). Although there was no clinical evidence of cardiotoxicity observed in any of the patients entered in the study, it should be emphasized that data from sequential gated blood pool scans are limited. An asymptomatic decrease in left ventricular ejection fraction was documented in two patients, and the potential cardiotoxicity of this regimen requires further study. Reassuringly, during previous investigations of this combination in patients with breast cancer, endomyocardial biopsies were performed and revealed that doxorubicin cardiotoxicity at doses of doxorubicin <360 mg/m² was not intensified by the coadministration of paclitaxel (26). Furthermore, the 96-h infusion doxorubicin schedule has less cardiotoxicity than that of bolus doxorubicin (15), further minimizing the risk of cardiac toxicity.

Previous studies of single-agent paclitaxel given by 96-h continuous i.v. infusion established that a $C_{\text{ss}}$ >60–70 nm was strongly correlated with the occurrence of severe neutropenia and mucosal toxicity (8, 9). In the present study, drug plasma levels were measured in four patients treated with paclitaxel 25 mg/m²/day in combination with 12.5 ($n = 3$) or 15.0 mg/m²/day ($n = 1$) doxorubicin, the two highest dose levels were evaluated. The paclitaxel $C_{\text{ss}}$ was found to be lower than the 60–70 nm threshold concentration for severe toxicity in each of these patients, ranging from 26.0 to 49.5 nm. This very likely accounts for the acceptable neutropenia, as well as other paclitaxel-related toxicities in this trial, and suggests that G-CSF may not be necessary. In fact, G-CSF has proven to be ineffective in controlling granulocyte toxicity when the paclitaxel $C_{\text{ss}}$ afforded by the 96-h infusion schedule exceeds 70 nm.

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mechanism of this interaction has not been definitively established, it appears to be a consequence of altered drug distribution, rather than an inhibitory effect upon P-glycoprotein-mediated biliary excretion or hepatic metabolism of doxorubicin (28, 30, 31). Differences in the plasma concentration-time profile of Cremophor EL imparted by the paclitaxel administration schedule could account for the apparent sequence or schedule-dependent effect upon doxorubicin pharmacokinetics. Increasing the duration of infusion to 72 h or longer, together with the administration of lower total doses than permitted by shorter infusion schedules of paclitaxel, may not provide sufficiently high systemic levels of Cremophor EL to modulate doxorubicin distribution.

The present study cannot differentiate the contribution of paclitaxel and doxorubicin to the efficacy of the regimen. However, the Cleveland Clinic group have recently published a Phase II study of 30 women receiving 96-h infusion paclitaxel for recurrent ovarian cancer (32). All patients were defined as resistant to paclitaxel. Although the regimen was well tolerated, no objective responses were observed. This is a disappointing result but in view of the activity seen in our study, perhaps strengthens the argument for a role for anthracyclines in advanced ovarian cancer. Although more patients on our study had been treated with paclitaxel in the first-line regimen, only 53% were clearly paclitaxel refractory. Despite the negative study by Markman et al. (32), there is sufficient confidence in the rationale for protruded exposure to paclitaxel that the GOG are conducting a randomized trial of i.v. cisplatin with either 24- or 96-h paclitaxel.

There was no attempt made in this study to escalate the dose of paclitaxel above 25 mg/m²/day; only the doxorubicin was escalated. Further increase of paclitaxel beyond the dose at the present MTD is unlikely to be successful. Indeed, a recent study by Fisherman et al. (33) of 72-h continuous infusion of paclitaxel and doxorubicin in patients with metastatic breast cancer defined a MTD of 60 mg/m²/day paclitaxel and 20 mg/m²/day doxorubicin with G-CSF support; however, this regimen had significant toxicity with dose-limiting diarrhea and neutropenia. Because the MTD of single-agent paclitaxel delivered over 96 h is 35 mg/m²/day with the DLT being mucositis (9), it is reasonable to anticipate that the potential for escalating the dose of paclitaxel beyond 25 mg/m²/day is limited. Prophylactic G-CSF was planned as part of the study design to ensure that the contribution of neutropenia to DLT was minimized in a combination of drugs that were likely to have myelosuppression as one of the major toxicities. Although neutropenia defined the MTD, at the MTD two patients experienced grade 4 thrombocytopenia, and it is possible that the use of G-CSF has contributed little to achievable dose intensity.

Recurrent ovarian cancer is an almost invariably fatal disease. Response rates from salvage chemotherapy regimens, including topotecan, hexamethylmelamine, ifosfamide, etoposide, and gemcitabine, range from 12 to 30% (2–7). In the present study, 5 of 15 evaluable patients responded to therapy. This is a particularly encouraging result in a Phase I study of heavily pretreated patients and includes a CR in a patient with recurrent disease after stem cell transplantation. The study is too small to speculate on a dose-response effect.

In summary, this study demonstrates that 12.5 mg/m²/day doxorubicin and 25 mg/m²/day paclitaxel can be safely delivered as an outpatient regimen over 96 h with acceptable toxicity when supported with G-CSF. Preliminary data demonstrate that this regimen has activity against relapsed epithelial ovarian cancer. The results of this Phase I study have encouraged us to further investigate the combination of paclitaxel and liposomal doxorubicin in a Phase II trial.

REFERENCES


A Phase I Study of Continuous Infusion Doxorubicin and Paclitaxel Chemotherapy with Granulocyte Colony-Stimulating Factor for Relapsed Epithelial Ovarian Cancer
