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SOUTHWEST ONCOLOGY GROUP TRIAL S9912: INTRAPERITONEAL CISPLATIN AND PACLITAXEL PLUS INTRAVENOUS PACLITAXEL AND PEGYLATED LIPOSOMAL DOXORUBICIN AS PRIMARY CHEMOTHERAPY OF SMALL- VOLUME RESIDUAL STAGE III OVARIAN CANCER

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Abstract

Objective—While primary cisplatin-based intraperitoneal chemotherapy has been shown to favorably impact survival in small-volume residual advanced ovarian cancer, there is a need to develop strategies that improve the effectiveness of this approach.

Methods—A multi-center phase 2 trial was conducted that added intravenous pegylated liposomal doxorubicin (day 8; 30–40 mg/m²) to a regimen of intraperitoneal cisplatin (day 2; 75 mg/m²) and intravenous (day 1; 135 mg/m²) plus intraperitoneal (day 8; 60 mg/m²) paclitaxel. Treatment was initially delivered on an every 3-week schedule, but was modified to an every 4-week program due to excessive toxicity. Patients were to receive 6 cycles of this regimen.

Results—Of 68 patients entering this trial, 63 patients were eligible and evaluable, of whom 39 (62%) completed 6 cycles. Overall, 32 (51%) experienced at least 1 grade 4 or worse toxicity (most commonly hematologic) including 5 treatment-related deaths. Median progression free survival

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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(PFS) was 25 months (2-year PFS: 52%) and median overall survival 51 months, an outcome similar to previous reports of cisplatin-based intraperitoneal chemotherapy in comparable patient populations. Seventeen patients (27% of all eligible patients) were without evidence of disease recurrence > 4 years following entry into the trial.

Conclusion—Both the overall trial outcome, and specifically the excessively severe systemic toxicity of this regimen would prevent its future development in this exact form. The provocative PFS in a subset of individuals should encourage the development of alternative strategies designed to optimize the delivery of regional therapy in ovarian cancer management.

INTRODUCTION

The results of several phase 3 randomized trials have revealed the favorable impact on survival associated with the intraperitoneal, compared to the systemic administration of cisplatin when employed as primary chemotherapy of small volume residual advanced epithelial ovarian cancer [1–4]. This outcome led to a decision by the National Cancer Institute to issue a “Clinical Announcement” regarding primary regional therapy in the management of this malignancy [5].

In the most recently reported phase 3 study, which demonstrated a median 16 month improvement in overall survival, paclitaxel was delivered by both the intravenous and intraperitoneal routes [3]. The results of this particular trial stimulated interest in the development of investigative strategies that build upon the foundation of an intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel regimen.

Pegylated liposomal doxorubicin has been shown to be biologically active and of clinical utility in platinum and paclitaxel resistant ovarian cancer [6,7]. An attraction associated with adding this specific agent to a cisplatin/paclitaxel combination is its lack of neurotoxicity [6,7]. Further, treatment with pegylated liposomal doxorubicin results in a *relatively modest degree* of bone marrow suppression, certainly compared to other cytotoxic agents commonly employed in this clinical setting [7–10].

This paper reports the results of a phase 2 front-line ovarian cancer chemotherapy trial conducted by the Gynecology Committee of the Southwest Oncology Group that added systemically-delivered pegylated liposomal doxorubicin to a cisplatin-based intraperitoneal program that also included the administration of both intravenous and intraperitoneal paclitaxel.

METHODS AND MATERIALS

Eligibility criteria

Patients considered eligible to enter this multi-center cooperative group phase 2 trial had to satisfy the following criteria: (a) histologically confirmed diagnosis of epithelial ovarian or primary peritoneal carcinoma; (b) previously undergone a staging exploratory laparotomy with an attempt at maximal surgical cytoreduction within 56 days prior to study entry and have optimal residual FIGO stage III disease (largest residual tumor nodule remaining within the peritoneal cavity ≤ 1 cm in maximal diameter); (c) no clinical evidence of residual disease by physical examination and chest radiograph within 28 days prior to registration; (d) no prior chemotherapy, immunotherapy, or pelvic radiotherapy for ovarian or peritoneal cancer; (e) SWOG performance status 0–2; (f) no evidence of active or uncontrolled infection, severe gastrointestinal symptoms (e.g., partial bowel obstruction), pre-existing neuropathy $\geq$ grade 2, or a history of a myocardial infarction or unstable angina in the 6 months prior to registration; and (g) serum bilirubin/SGOT (or SGPT) ≤ 2 times institutional upper limit of normal,

granulocyte count $\geq 1,500/\text{uL}$, platelets $\geq 100,000/\text{uL}$, and calculated creatinine clearance $\geq 50 \text{ cc/min}$ within 28 days prior to registration. Patients with borderline or low malignant potential ovarian malignancies, and individuals with a history of any cancer (except adequately treated basal cell or squamous cell skin cancer) from which they had been disease-free for < 5 years were not eligible for entry into this clinical trial.

All patients entered into this study were informed of its investigational nature and were required to sign an institutional review board approved consent form that satisfied federal guidelines.

Treatment plan

For those patients with obvious, advanced ovarian or primary peritoneal cancer before registration it was possible to obtain informed consent prior to the performance of the cytoreductive surgery with placement of an indwelling catheter at that time if the patient was confirmed to satisfy all eligibility criteria (e.g., confirmed appropriate histology, small volume residual disease). Alternatively, a patient could be entered into the study following surgery, which would require the subsequent placement of a drug delivery device.

The chemotherapy program is outlined in Table 1 (*Original Dose/Schedule*). Patients also received standard pre-medications for cisplatin and paclitaxel containing chemotherapy, and necessary hydration. After 2 cycles at a particular level, the dose of pegylated liposomal doxorubicin was to be escalated (see Table 1), assuming no grade 3 hematologic toxicities lasting > 5 days, no $> \text{grade } 2$ stomatitis, and no $> \text{grade } 1$ hand-foot skin reactions with the prior cycles. The treatment protocol defined specific dose modifications and criteria for withholding day 8 therapy based on any observed toxicity.

Bone marrow hematopoietic factors were not routinely employed in this trial. Study participants were permitted to receive granulocyte colony stimulating factor (G-CSF) where clinically-indicated for reasons of patient safety. In the setting of excessive neutropenia observed during the initial treatment cycle, the next cycle was to be delivered with a dose reduction (and without prophylactic G-CSF). However, if excessive neutropenia was still observed, subsequent treatment cycles were to be administered with prophylactic G-CSF.

For patients who did not experience unacceptable toxicity or disease progression a maximum of 6 cycles of treatment were to be delivered, with subsequent observation. With the documentation of disease progression the patient was removed from the study and was able to receive alternative management strategies.

Following the treatment of 9 patients with this experimental treatment regimen it was determined that toxicity (principally hematologic) was excessive (Table 2A). As a result, treatment on the protocol was temporarily suspended. The study was subsequently reopened with several major changes designed to reduce the severity of therapy-induced marrow suppression (Table 1, *Modified Dose/Schedule*). The modifications included: (a) delivery of the treatment cycles on a *4-weekly* rather than a 3-weekly schedule; (b) administration of intravenous paclitaxel (day 1) as a *3-hour* rather than a 24-hour infusion;

Statistical considerations

The primary objective of this phase 2 study was to evaluate the progression-free survival (PFS) and overall survival of optimally cytoreduced ($\leq 1 \text{ cm}$) stage III ovarian or primary peritoneal cancer patients treated with the chemotherapy regimen described above (Table 1). Based on previously published data from a Southwest Oncology Group/Gynecologic Oncology Group randomized phase 3 trial cisplatin-based intraperitoneal chemotherapy employed as primary treatment of ovarian cancer patients with the same eligibility criteria as regards the extent of

residual cancer following initial surgery, this population was estimated to have an anticipated median PFS of 2.3 years and a 2-year PFS rate of 55% [2].

Compared to this background data, it was judged that a 50% increase in median PFS (to 3.5 years) would render the study regimen of definite interest for further pursuit, provided the overall survival and toxicity were also favorable. Assuming an exponential distribution, a 50% increase in median corresponds to a 12% increase from 55% to 67% in the 2-year PFS rate.

The sample size target was 62 eligible individuals over 4 years. Patients were to be followed for 2 additional years before the final analysis was performed. With a one-sided Brookmeyer and Crowley 95% confidence interval for median PFS [11], the power to reject the null hypothesis (i.e., median = 2.3 years) was approximately 80% if the true median was 3.5 years [11]. This calculation assumes exponential PFS distributions and uniform patient entry.

In addition, the planned sample size was sufficient to estimate the probability of a particular toxicity to within $\pm 12\%$. Further, any toxicity occurring with at least a 5% probability would almost certainly (96% chance) be seen at least once.

Progression-free survival and overall survival estimates were calculated using the method of Kaplan-Meier [12]. All statistical analyses were performed using SAS version 9.0.

Definition of disease progression

Progression of disease on this protocol was defined by any one of the following criteria: (a) clear worsening of any measurable/evaluable disease; (b) reappearance of any lesion that had disappeared; (c) appearance of any new lesion/site; and (d) death or deteriorating condition that was *not* specifically evaluated and was *not* determined to be clearly unrelated to this cancer. The following CA-125 criteria were also acceptable as evidence of disease progression: (a) patients with elevated baseline CA-125 (> 35 U/ml) and subsequent normalization (≤ 35 U/ml) of CA-125 must show evidence of CA-125 > 2 -times the upper limit of normal (> 70 U/ml) on 2 occasions at least 1 week apart; (b) patients with elevated baseline CA-125 (> 35 U/ml) which never normalizes must show evidence of CA-125 > 2 -times the nadir value on 2 occasions at least 1 week apart; (c) patients with baseline CA-125 in the normal range (≤ 35 U/ml) must show evidence of CA-125 > 2 times the upper limit of normal (> 70 U/ml) on 2 occasions at least 1 week apart.

To be considered as evidence of recurrent disease, any ascites or pleural effusion needed to be documented to be cytologically positive for malignant cells. Further, it was strongly recommended (but not required) that solid tumor nodules were biopsied to document disease recurrence.

RESULTS

Sixty-eight patients were enrolled on this phase 2 study, of which 5 individuals were subsequently determined to be ineligible. The median age of the treated population was 59 (range 34–80).

Sixty-three patients were evaluable for adverse events (Tables 2A, 2B). There were 5 treatment-related deaths, 4 of which occurred in patients treated with the modified paclitaxel and liposomal doxorubicin regimen after the previously described temporary closure of the study. These deaths resulted from: aspiration pneumonia (1 case); cardiac ischemia, 2 days after treatment (1 case); peritonitis (1 case); and sepsis (2 cases).

Overall, 32 patients (51%) experienced at least one grade 4 or 5 toxicity, with the most common serious side effects being hematologic (41% of all patients). In the original treatment schedule (prior to study modification) 7 of the 9 individuals receiving this regimen experienced ≥ 1 grade 4 or 5 toxicity.

Thirty-nine (62%) patients completed the entire planned treatment regimen, while 16 (25%) were removed for the development of serious adverse events. Information related to the number of patients who were able to have the dose of pegylated liposomal doxorubicin increased was not specifically captured in the reporting of study data, but in view of the severe hematologic toxicity observed in the trial such dose escalation (if it occurred at all) was likely to have been infrequent.

The median PFS was 2.1 years (95% confidence interval: 1.6–2.8 years). The 2-year PFS was 52% (95% confidence: 40%–65%). The estimated median overall survival is 4.3 years (95% confidence interval: 3.5–4.9 years). At the time of publication, 17 individuals (27% of all eligible patients) were without evidence of recurrence of disease > 4 years following entry into this phase 2 trial.

DISCUSSION

Several reasonable conclusions can be drawn from the results of this relatively large phase 2 multi-center cooperative group trial that explored the addition of systemically-administered pegylated liposomal doxorubicin to a cisplatin-based intraperitoneal program employed as primary treatment of small-volume residual advanced epithelial ovarian cancer.

First, while the study demonstrated the ability to add pegylated liposomal doxorubicin to a cisplatin-based intraperitoneal chemotherapy program, this modification in the treatment strategy substantially increased the risk of clinically-relevant adverse events, particularly excessively severe bone marrow suppression. In fact, even following the modification in the regimen designed to reduce the severity of such side effect, 20 of 54 patients (37%) experienced grade 4 hematologic toxicity.

These data are consistent with previously reported experiences that have attempted to combine a “third cytotoxic” drug within the *same cycle* (versus, for example, the delivery of this “added” agent in alternating or sequential cycles) of a two-drug platinum-based ovarian cancer combination chemotherapy program [13–15]. In fact, in the development of the recently reported large international multi-arm phase 3 randomized trial that included the triplet regimen of carboplatin plus paclitaxel and pegylated liposomal doxorubicin, the pegylated liposomal doxorubicin was only able to be administered every other treatment cycle (on a 6 week versus 3 week schedule) [16].

Second, the study failed to demonstrate a prospectively-defined improvement in median PFS, its primary endpoint. While provocative long-term PFS (27% at > 4 year follow-up) was observed among patients treated on this phase 2 trial it remains unknown if this outcome was due to treatment with this *specific* novel treatment regimen, or might have occurred following delivery of other chemotherapy programs due to major inherent chemosensitivity of this specific subgroup of individuals. Only the results of a subsequently conducted randomized phase 3 study can appropriately address this important question.

Third, it is relevant to acknowledge the rather striking heterogeneity of the toxicity profile observed within this multi-center phase 2 trial. While a substantial risk of side effects (principally hematologic) was noted, 17% of patients receiving the “modified regimen” were able to be treated without developing a single grade 3 adverse event, and an additional 37% without an episode of grade 4 toxicity.

It will be important for future research efforts to be undertaken to more fully understand the reasons for this heterogeneity, whether related to underappreciated co-morbidity or other factors. The aim here would be to define individuals who would be appropriate candidates for such a therapeutic regimen, while selecting alternative strategies if excessive side effects are predicted. One reasonable suggestion for future investigative efforts is the hypothesis that patients who experience particularly slow recovery following their initial cytoreductive surgery that results in delayed discharge from the hospital or resumption of activities of daily living may be particularly poor candidates for a subsequently delivered intensive systemic treatment strategy, even if they “technically” satisfy all study eligibility criteria.

Currently, there are several cooperative group efforts planned to further evaluate regional drug delivery in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer. A particular focus of these trials is the very reasonable goal to *reduce the observed side effects* associated with both intraperitoneal therapy itself, and the administration of cisplatin.

However, it is appropriate to also emphasize the importance of exploring strategies designed to *enhance the already demonstrated efficacy* associated with this specific route of drug delivery, while simultaneously preventing the development of excessive toxicity (as unfortunately observed in the current trial).

Hopefully, by rationally combining anti-neoplastic agents (e.g., platinum/paclitaxel/anti-angiogenic agents, etc.) with additive or synergistic favorable biological effects that can be optimized with some (or all) of the drugs delivered via the intraperitoneal route, the outcome for women with advanced ovarian cancer will be improved. Based on existing data regarding the demonstrated favorable impact on survival associated with regional treatment of ovarian cancer it is reasonable to conclude that exploration of such approaches should be a priority of the gynecologic cancer clinical research community [1–5].

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Figure 1.
Progression-free survival (PFS)

Figure 2.
Overall survival

TABLE 1
TREATMENT SCHEMA (INITIAL AND MODIFIED)

Drug	Original Dose/Schedule (n=9 patients)	Modified Dose/Schedule (n=54 patients)
IV paclitaxel	135 mg/m ² over 24 hours day 1 q 3-weeks × 6 cycles	135 mg/m ² over 3 hours day 1 q 4 weeks × 6 cycles
IP cisplatin	75 mg/m ² day 2 q 3-weeks × 6 cycles	75 mg/m ² day 2 q 4 weeks × 6 cycles
IP paclitaxel	60 mg/m ² day 8 q 3-weeks × 6 cycles	60 mg/m ² day 8 q 4 weeks × 6 cycles
IV pegylated liposomal doxorubicin	30 mg/m ² q 3 weeks day 8 × 2 cycles 35 mg/m ² q 3 weeks day 8 × 2 cycles 40 mg/m ² q 3 weeks day 8 × 2 cycles	30 mg/m ² q 4 weeks day 8 × 2 cycles 35 mg/m ² q 4 weeks day 8 × 2 cycles 40 mg/m ² q 4 weeks day 8 × 2 cycles

Table 2

TABLE 2-A. TREATMENT-RELATED ADVERSE EVENTS PRIOR TO MODIFICATION OF TREATMENT REGIMEN (n = 9 patients)				
<i>Adverse Events</i>	<i>Grade</i>			
	2	3	4	5
Cardiovascular	1			
Dermatologic	4	1		
Flu-like symptoms	2	2	1	
Gastrointestinal	3	3	2	
Hematologic		3	6	
Infection	1	3	2	
Lung		2		1
Metabolic		1		
Neurologic			1	
Pain				
Renal/bladder	1	1		
Maximum grade (any event)		2	6	1
TABLE 2-B. TREATMENT-RELATED ADVERSE EVENTS FOLLOWING MODIFICATION OF CHEMOTHERAPY REGIMEN (n = 54 patients)				
<i>Adverse Events</i>	<i>Grade</i>			
	2	3	4	5
Cardiovascular	2	6	1	1
Dermatologic	34	2		
Flu-like symptoms	17	8	1	
Gastrointestinal	17	18	2	
Hematologic	9	15	20	
Infection	3	12	1	3
Lung	9			
Metabolic	8	6	2	
Neurologic	12	5		
Pain	16	8		
Renal/bladder	1		1	
Maximum grade (any event)	8	20	21	4