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A phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: A Gynecologic Oncology Group study

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Abstract

Purpose—To determine the first-cycle maximum tolerated dose (MTD) of intraperitoneal carboplatin in combination with intravenous paclitaxel and then assess the feasibility of this dose over multiple cycles.

Methods—Beginning at an intraperitoneal (IP) carboplatin dose area under the curve (AUC) of 5 and a fixed intravenous dose of 175 mg/m² paclitaxel, patients were entered on a dose-escalating phase evaluating first-cycle dose-limiting toxicity (DLT). After estimating the MTD, cohorts of 20 patients were then entered in an expanded phase to evaluate DLT over four cycles.

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CONFLICT OF INTEREST STATEMENT

The authors wish to report that they have no conflicts of interest.

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Results—Twenty-one patients were entered on the dose-escalating phase. A first-cycle MTD of carboplatin at AUC 8 was tolerated although thrombocytopenia was dose-limiting over multiple cycles. An additional 69 patients were treated in expanded cohorts. Only 5/90 (5.6 %) patients discontinued treatment because of a port problem. Four-cycle DLT required de-escalation to a carboplatin AUC of 6, and even at that dose, there were 14 dose-limiting toxic effects in 40 patients (35%). Seven dose-limiting toxicities were due to neutropenia and 6 were due to grade 3/4 thrombocytopenia. Six cycles of therapy were completed in 75% of eligible patients but dose adjustments were required.

Conclusions—The first-cycle MTD did not predict the tolerability of this regimen over multiple cycles. Using an IP carboplatin dose of AUC 6 in combination with paclitaxel, the regimen can be administered with a high completion rate over multiple cycles. Because neutropenia is a frequent DLT, the addition of hematopoietic growth factors may permit a high completion rate while maintaining this dose.

Keywords

phase I trial; intraperitoneal chemotherapy; ovarian cancer; chemotherapy; carboplatin

INTRODUCTION

Cytoreductive surgery followed by combined platinum and taxane chemotherapy is the accepted standard treatment for patients with advanced epithelial ovarian cancer (1). In patients with small volume residual disease, three large randomized Phase III studies comparing intraperitoneal (IP) to intravenous (IV) cisplatin-based chemotherapy have reported favorable survival results for the IP arms (2,3,4). Despite this, IP cisplatin-based chemotherapy has not been widely utilized as a standard treatment because of issues regarding toxicity and difficulties with administration. Although IV administration of carboplatin is as efficacious as cisplatin but less toxic, early studies have suggested inferiority of IP carboplatin (5,6). However, pharmacological data now show that more than 2/3 of free platinum enters into the systemic circulation after IP carboplatin administration, and Miyagi, *et al.* demonstrated that the 24-hour free platinum area under the curve (AUC) in the serum was identical with IP or IV administration (7,8). Concentrations may be even higher in retroperitoneal lymph nodes (9). A Japanese study found that patients treated with greater than 400 mg/m² of IP carboplatin had a significantly longer survival than patients treated with lesser doses (10). A Greek Phase III trial of IP or IV carboplatin at 350 mg/m² with intravenous cyclophosphamide showed excellent response rates (75%) and equivalent survival (11).

In an effort to find a less toxic intraperitoneal chemotherapy regimen the Gynecologic Oncology Group (GOG) initiated a series of Phase I trials evaluating regimens utilizing IP carboplatin. We report the results of an international, multi-institutional Phase I trial of intraperitoneal carboplatin combined with intravenous paclitaxel in women with chemotherapy-naïve ovarian, primary peritoneal, or fallopian tube cancer. This study evaluates the combination of intraperitoneal carboplatin with intravenous paclitaxel, with the goal of determining the optimal dose of IP carboplatin to be used with IV paclitaxel in a randomized Phase III trial. Recognizing that a Phase I maximum tolerated dose (MTD) based on first-cycle dose-limiting toxicity (DLT) may not determine a dose that is acceptable over many cycles in a Phase III trial, we used an expanded cohort methodology to explore the effect of the regimen given at first-cycle MTD over multiple cycles.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients had to be ≥ 18 years of age and have previously-untreated stage II, III or IV, epithelial ovarian, primary peritoneal or fallopian tube carcinoma regardless of residual disease following surgery. A GOG Performance Status of ≤ 2 was required and patients were entered within 12-weeks of surgery. Patients had to have adequate bone marrow function (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$), renal function (creatinine $\leq 1.5 \times$ institutional upper limit normal (ULN)), hepatic function (bilirubin $\leq 1.5 \times$ ULN, ALT, AST, and alkaline phosphatase $\leq 2.5 \times$ ULN) and neurologic function (sensory or motor neuropathy $\leq$ grade 1). After Institutional Review Board approval, written informed consent consistent with all federal, state and local requirements was obtained from all patients before study entry.

Treatment Plan

On day one of each 21-day treatment cycle, paclitaxel was administered as a three hour IV infusion. The paclitaxel dose was kept constant at 175 mg/m^2 . One liter of saline or 5% dextrose in water was infused IP during or after the IV paclitaxel. This was followed by the IP administration of carboplatin at the assigned dose in 100 cc to 1000 cc of normal saline as rapidly as possible (usually 15 minutes). The IP carboplatin dose was started at an AUC 5 and was calculated by the Calvert formula with the creatinine clearance being estimated by the method of Jelliffe (12). The volume used for the IP carboplatin was left to the investigator's discretion based on body size (1000 cc recommended). No attempt was made to drain the infusate, although ascites could be drained prior to infusion if a large amount was present. Routine premedication to prevent hypersensitivity, nausea, or vomiting was used and included dexamethasone, diphenhydramine and cimetidine. Ondansetron or granisetron were suggested as antiemetics given prior to the IP carboplatin. Patients could receive up to eight cycles of therapy during the dose-seeking phase, but the protocol was amended to only allow a maximum of six cycles for the expanded phase. Commercially available carboplatin (Paraplatin®, Bristol-Myers Squibb Oncology) and paclitaxel (Taxol®, Bristol-Myers Squibb Oncology) were used.

Evaluation During Study

Pretreatment evaluation consisted of a history and physical examination, chest x-ray, complete blood count, prothrombin time, activated partial thromboplastin time, CA-125 testing, serum electrolytes, creatinine, liver function tests, electrocardiogram. A baseline imaging study (computed tomography scan or magnetic resonance imaging of the abdomen and pelvis) was performed in patients with greater than 1 cm residual nodules after surgery. Complete blood function tests were obtained prior to each cycle. The FACT/GOG-NTX questionnaire was administered after each cycle to evaluate neurotoxicity. Patients were also examined prior to every cycle. Measurable lesions noted at baseline were reevaluated after cycles 4 and 8 during the dose escalation phase and after cycles 3 and 6 in the expanded phase. Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess response (13). Patients were followed for one year after treatment.

Dose-Limiting Toxicity

In accordance with the NCI Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE v3), DLT was defined as either hematologic or non-hematologic toxicity which occurred in the first cycle during the dose-seeking phase (or in the first 4 cycles in the expanded phase). Hematologic DLT included a dose delay of > 2 weeks due to failure to recover counts adequately (see Dose Adjustments), study-treatment-related febrile

neutropenia (fever ≥ 38.5 °C) when the absolute neutrophil count (ANC) is $<1.0 \times 10^9/L$, Grade 4 neutropenia lasting ≥ 7 days and Grade 3 or 4 thrombocytopenia. Non-hematologic DLT included study-treatment-related grade 3 or 4 toxicities (excluding fatigue, hypersensitivity reaction, nausea and vomiting) or any drug-related death.

Dose Adjustments

Initial treatment modifications consisted of cycle delay and dose reduction. Subsequent cycles of therapy could not begin until the ANC was $\geq 1.5 \times 10^9/L$ (NCI-CTC Grade 1) and the platelet count was $\geq 75 \times 10^9/L$. Therapy could be delayed for a maximum of two weeks until these values were achieved otherwise the patient was removed from study. Two dose reductions of IP carboplatin were allowed for grade 3 or 4 thrombocytopenia, or thrombocytopenia-associated bleeding that required a platelet transfusion. One dose-reduction of IV paclitaxel was allowed for febrile neutropenia and/or grade 4 neutropenia lasting ≥ 7 days. Dose modifications were not made for anemia. Patients could receive red blood cell transfusions and/or erythropoietin using standard supportive care guidelines. Other hematologic growth factors were allowed after the above dose adjustments at the discretion of the treating physician.

Dose delay up to two weeks was allowed and modification was required for any drug-related grade 3 or 4 non-hematologic toxicity. Treatment was discontinued in patients with persistent peripheral neuropathy $\geq$ grade 3. Persistent grade 2 neuropathy required a one time dose reduction of paclitaxel. Otherwise, patients with non-hematologic toxicity had to return to $\leq$ grade 1 before continuing therapy.

Statistical Considerations

The study was carried out in two phases. The dose-seeking phase was designed to find the MTD of the study regimen and utilized a standard 3+3 phase I design. Doses were escalated to next planned dose if 0/3 or 1/6 patients experienced DLTs. Once an estimate of the MTD was established, the second “expanded phase” was initiated.

A two-stage sequential design was used in the expanded phase to assess the feasibility of delivering multiple cycles of the study regimen. The decision rules for whether or not to advance to the next stage of the study are summarized in Table 1. Based on the estimated frequency of dose modification and/or delay with the two-drug combination of carboplatin and paclitaxel in Protocol GOG-158 (14), the regimen in this study would be considered *not* feasible for a Phase III study if the true event (DLT) probability within the first 4 cycles of therapy was $\geq 40\%$. If the true event rate for this regimen was 40%, this design provided a 91% chance of classifying the regimen as not feasible, with a 58% chance reaching this conclusion before beginning the second stage. If the event rate was as low as 20%, the design provided a 91% chance of classifying the regimen as feasible and a 63% chance of reaching this conclusion before beginning the second stage.

RESULTS

Patient Characteristics

A total of 90 patients were entered on the trial from June 2004 until June 2008. Twenty-one patients were entered on the dose-seeking phase (evaluating cycle 1 toxicity). One patient was ineligible for toxicity evaluation due to a wrong starting dose and another did not receive protocol therapy due to an IP catheter malfunction. Sixty-nine patients were entered on the expanded phase (evaluating 4-cycle toxicity). Nine patients were not evaluable for four-cycle toxicity (4 had hypersensitivity reactions to paclitaxel before cycle #4, three had progression of disease before cycle #4 and two were treated at the wrong dose).

Demographics for all 90 patients entered on study are listed in Tables 2 and 3. Toxicity is only reported for 19 evaluable patients in the dose-seeking phase and 60 evaluable patients in the expanded phase (20 at AUC 7 and 40 at AUC6).

Dose Escalation Phase: Toxicity

IP Carboplatin AUC 5—Of the three patients treated there were no first-cycle DLTs and all received eight cycles. One had a dose reduction after cycle #5 for grade 3 thrombocytopenia.

IP Carboplatin AUC 6—Of the four eligible patients treated there were no first-cycle DLTs and three patients completed eight cycles. One of these three patients had a dose reduction of paclitaxel for febrile neutropenia after cycle # 7 and the fourth patient had a port malfunction after the first cycle and was removed from study.

IP Carboplatin AUC 7—Of the six eligible patients treated, there was 1 first-cycle DLT (grade 4 thrombocytopenia). However, only one patient completed eight cycles. Three were removed from study for a > 2 week delay in recovering blood counts (after cycle #2, 5, 6), one was removed after cycle # 1 due to persistent grade 2 neuropathy and another was removed for a hypersensitivity reaction to paclitaxel after cycle #3.

IP Carboplatin AUC 8—Of the six patients treated, there was one first-cycle DLT (grade 3 thrombocytopenia). That patient was removed from study after cycle #2 due to grade 4 thrombocytopenia despite dose-reduction. Only one patient completed 8 cycles and she had a dose reduction of IP carboplatin after cycle #2 due to grade 3 thrombocytopenia (Table 4). Three patients were removed for a > 2 week delay in recovering blood counts and one other patient was removed after cycle #4 due to an IP port infection.

Expanded Phase: Rationale for dose selection—Since there was only one first cycle DLT in six patients treated at an IP carboplatin dose AUC 8, dose escalation to AUC 9 was considered. However, on reviewing the results of patients treated at an AUC of 7 and 8, only two of twelve patients were able to complete the planned regimen of 8 cycles and both patients required a dose reduction by cycle #4 (grade 3, 4 thrombocytopenia). Also, nine of twelve patients had a DLT by cycle #4, and six patients were removed from study due to a > 2 week delay in recovering blood counts. Since the goal of the study was to determine the tolerability of treatment over multiple cycles, escalation to an AUC of 9 was not felt prudent. The expanded phase was therefore opened at an IP carboplatin AUC of 7 with plans to escalate or de-escalate based on the results. The total number of planned cycles was also reduced to six to be consistent with the standard recommended cycle number for intravenous carboplatin and paclitaxel on other GOG trials.

Expanded Phase: Toxicity

IP Carboplatin AUC 7—Twenty-two patients were entered and two were not eligible for 4-cycle toxicity evaluation due to hypersensitivity reactions to paclitaxel in the first cycle. Of the 20 eligible patients treated, there were nine DLTs within four cycles. Table 4. There was one death due to neutropenic sepsis associated with a *c. difficile* infection after cycle #1. There were four DLTs due to a delay of > two weeks to recover neutrophil counts, two due to neutropenic fever (including the death), two due to grade 3 or 4 thrombocytopenia and one due to grade 4 metabolic toxicity. Given that there were greater than eight DLTs, this regimen was not considered feasible for a Phase III trial. In addition, there was only 1 IP port problem (port abscess requiring removal) and 11 patients (55%) completed six cycles.

IP Carboplatin AUC 6—Forty-seven patients were entered and seven were not eligible for four-cycle toxicity evaluation (two treated at wrong dose, two hypersensitivity reactions to paclitaxel in first cycle, two progression of disease by cycle 3 and one patient refused IP therapy after the first cycle). Of the 40 eligible patients treated, there were 14 DLTs. There were six DLTs due to grade 3 or 4 thrombocytopenia, four DLTs due to a delay of > 2 weeks to recover neutrophil counts, two DLTs due to neutropenic fever, one grade 4 neutropenia > 7 days and one DLT due to grade 3 mental status changes requiring hospitalization. Thirty (75%) patients completed six cycles of IP therapy with dose adjustments after cycle #4 when required by protocol. There were two IP port malfunctions. Both were replaced and both patients completed six cycles. The highest grade of toxicity for each of the 40 evaluable patients is listed in Table 5.

Response Rates and Progression

Response rates and data regarding progression were evaluated for patients treated at an AUC 6 in the expanded phase. An intent-to-treat analysis revealed that of all 47 patients entered at an AUC 6, 14 (30%, 95% CI 17%–45%) had disease progression within one year of initiating protocol treatment. Two patients had progression of disease before cycle #4. Of the 35 patients treated at an AUC 6 who completed at least four cycles of protocol therapy, nine (26%, 95% CI, 12%–43%) had evidence of disease progression within one year of initiating therapy. Four of 35 patients (11%) had suboptimal disease. However, only two of those patients had measurable disease on radiologic imaging and both had a complete clinical response after treatment.

DISCUSSION

The GOG has sought to develop regimens using IP carboplatin for use in a Phase III trial comparing systemic carboplatin and paclitaxel to intraperitoneal chemotherapy. Retrospective evaluation of the experience with IP carboplatin and IV paclitaxel (175mg/m²) as primary treatment of ovarian, peritoneal or fallopian tube cancer in Japan confirms that myelotoxicity, especially thrombocytopenia, appears to be dose-limiting (15). In the study reported here, Grade 4 neutropenia was seen in 63% of patients treated at an IP carboplatin AUC of 6. Grade 3 or 4 thrombocytopenia was only seen in 15% of patients at this dose, but was always considered dose-limiting. In GOG-158, 72% grade 4 neutropenia and 39% grade 3 and 4 thrombocytopenia were observed in patients treated with IV paclitaxel (175 mg/m²) and IV carboplatin (AUC=7.5)(14).

The most recently reported GOG randomized trial of intraperitoneal chemotherapy (GOG 172), demonstrated a relative risk of recurrence of 0.73 and a 15.9 month improvement in overall survival with the IP regimen. This was despite the fact that only 42% of patients completed the planned six cycles IP and 49% in the IP arm received three or fewer IP treatments (3). IP catheter problems occurred in 34% of patients and were a major reason for discontinuing IP therapy (16). In the study reported here, only 7/90 (8%) of patients entered had problems related to the IP catheter and five were responsible for discontinuing IP therapy. This low rate may be due to the use of IP carboplatin alone, more common placement of catheters at the time of initial surgery or more experienced surgeons and staff participating in Phase I trials with the GOG. The progression rate at one year (30%) for the expanded cohort treated at a carboplatin dose of AUC 6 is comparable to GOG 172 where 25% of patients had disease progression in one year (3).

This Phase I trial established that the first cycle MTD of IP carboplatin was at least an AUC of 8 when given every three weeks with paclitaxel at 175 mg/m². However, follow-up of patients on the dose-seeking phase treated beyond the first cycle revealed that it was unlikely that multiple cycles would be tolerated at the MTD. In the expanded phase,

evaluating four-cycle toxicity, even an AUC 7 was not considered feasible in a Phase III trial. At a carboplatin AUC 6, 13/14 DLTs were due to myelosuppression: six due to thrombocytopenia and seven due to leukopenia or neutropenia.

Although not feasible for incorporation into a Phase III trial based on the criteria of this study, the regimen of IP carboplatin at an AUC 6 with IV paclitaxel at 175 mg/m² is well tolerated over multiple cycles with a high six cycle completion rate (75%). Serious outcomes associated with myelosuppression, such as febrile neutropenia or bleeding were infrequent. The pattern of DLTs suggest that with broadened criteria for dose delay or incorporation of granulocyte colony-stimulating factors, this dose could be feasible in a Phase III trial.

The GOG has recently opened a randomized trial comparing IV and IP chemotherapy (Figure 1, online only). All regimens will also contain bevacizumab during treatment and for 11 months after chemotherapy. The IP carboplatin dose chosen is an AUC of 6, combined with IV paclitaxel (80 mg/m²) on days 1, 8 and 15 based on recent trial suggesting improved survival and comparable toxicity with the dose-dense regimen versus the standard three week IV regimen (17). Given the survival advantage of IP therapy in the treatment of women with ovarian, fallopian tube, and primary peritoneal carcinoma, it is hoped that findings from this study which have been incorporated into the ongoing GOG trial will make this therapy equally efficacious and more tolerable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Expanded phase* = DLT

Stage	Cumulative Accrual	Maximum # of events* to stop the study and consider the regimen feasible for phase III	Minimum # of events* to stop the study and consider the regimen not feasible for phase III
1	20	4	8
2	40	11	12

* Events = Dose limiting toxicity

Table 2

Demographics. Dose escalation phase (n=21)

Characteristic	Category	Number	% of Cases
Age (years)	17–49 years	2	10
	50–59 years	7	33
	60–69 years	8	38
	70–79 years	4	19
	80–89 years		
Ethnicity	Hispanic	1	5
	White	18	85
	Asian	2	10
	Black	0	
Performance Status	0	14	66
	1	4	19
	2	3	15
Site of Disease	Ovary	18	85
	Fallopian tube	0	
	Primary Peritoneal	3	15
Stage	IIb	0	
	IIc	0	
	IIIa	4	19
	IIIb	1	5
	IIIc	15	71
	IV	1	5
Debulking	Optimal	14	67
	Suboptimal > 1cm	7	33
Measurable Disease	No	14	67
	Yes	7	33

Table 3

Demographics. Expanded Cohorts AUC 6 and 7 (n=69)

Characteristic	Category	Number	% of Cases
Age (years)	17–49 years	13	19%
	50–59 years	18	26%
	60–69 years	26	38%
	70–79 years	11	16%
	80–89 years	1	1%
Ethnicity	Hispanic	3	4%
	White	58	84%
	Asian	7	10%
	Black	1	1%
Performance Status	0	35	51%
	1	29	42%
	2	5	7%
Site of Disease	Ovary	52	75%
	Fallopian tube	4	6%
	Primary Peritoneal	13	19%
Stage	IIb	2	3%
	IIc	6	9%
	IIIa	2	3%
	IIIb	6	9%
	IIIc	46	67%
	IV	7	10%
Debulking	Optimal	57	83%
	Suboptimal > 11cm1cm1cm	12	17%
Measurable Disease	No	60	87%
	Yes	9	13%

Table 4

Toxicity at AUC 8 in dose-escalating phase (N=6)

Adverse Effect	GRADE					Total
	0	1	2	3	4	
Leukopenia	0	0	0	6	0	6
Thrombocytopenia	0	0	1	4	1	6
Neutropenia	0	0	0	0	6	6
Anemia	0	0	4	2	0	6
Cardiovascular	5	0	1	0	0	6
Constitutional	1	2	3	0	0	6
Dermatologic (not alopecia)	4	0	2	0	0	6
Gastrointestinal	0	1	4	1	0	6
Genitourinary/Renal	4	1	0	1	0	6
Hepatic	5	1	0	0	0	6
Infection/neutropenic	5	0	0	1	0	6
Infection/hot neutropenic	4	0	0	2	0	6
Metabolic	2	3	1	0	0	6
Neuropathy-sensory	0	6	0	0	0	6
Neuropathy-other	5	0	1	0	0	6
Pain (Abdominal)	1	3	1	1	0	6

Table 5

Toxicity in expanded phase cohort AUC 7 (N=20)

Adverse Effect	GRADE					
	0	1	2	3	4	Total
Leukopenia	0	1	3	11	5	20
Thrombocytopenia	2	9	2	4	3	20
Neutropenia	0	1	1	2	16	20
Anemia	0	2	13	5	0	20
Cardiovascular	13	4	2	1	0	20
Constitutional	2	3	13	1	1	20
Dermatologic (not alopecia)	12	8	0	0	0	20
Gastrointestinal	0	6	11	2	1	20
Genitourinary/Renal	15	1	2	1	1	20
Hepatic	13	5	2	0	0	20
Infection/neutropenic	15	0	1	3	1	20
Infection/hot neutropenic	14	1	2	3	0	20
Metabolic	7	5	4	4	0	20
Neuropathy-sensory	8	10	2	0	0	20
Neuropathy-other	7	5	7	1	0	20
Pain (Abdominal)	10	6	4	0	0	20

Table 6

Toxicity in expanded phase cohort AUC 6 (N=40)

Adverse Effect	GRADE						Total
	0	1	2	3	4	5	
Leukopenia	0	5	16	18	1		40
Thrombocytopenia	13	13	8	2	4		40
Neutropenia	0	0	4	11	25		40
Anemia	1	14	17	7	1		40
Cardiovascular	28	7	5	0	0		40
Constitutional	4	21	14	1	0		40
Dermatologic (not alopecia)	28	11	1	0	0		40
Gastrointestinal	4	20	10	6	0		40
Genitourinary/Renal	39	0	1	0	0		40
Hepatic	16	12	0	2	0		40
Infection/neutropenic	36	0	0	3	1		40
Infection/hot neutropenic	29	0	8	3	0		40
Metabolic	19	17	1	3	0		40
Neuropathy-sensory	6	21	9	4	0		40
Neuropathy-other	26	7	3	4	0		40
Pain (Abdominal)	18	12	5	5	0		40