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

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Abstract

Objective—To define the maximum tolerated dose (MTD) and assess the feasibility of intravenous (IV) docetaxel, intraperitoneal (IP) carboplatin and IP paclitaxel in women with Stage II-IV untreated ovarian, fallopian tube or primary peritoneal carcinoma.

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Methods—Patients received docetaxel (55-75 mg/m^2) IV and carboplatin (AUC 5-7) IP on day 1 and paclitaxel 60 mg/m^2 IP on day 8. A standard 3+3 design was used in the dose escalation phase. A 2-stage group sequential design with 20 patients at the MTD was used in the feasibility phase.

Results—The MTD determined during the dose escalation phase was day 1 docetaxel 75 mg/m^2 IV, carboplatin AUC 6 IP and day 8 IP paclitaxel 60 mg/m^2. Forty-six patients were enrolled in the feasibility portion at this dose level. Six were unevaluable. Fifteen evaluable patients had dose-limiting toxicities (DLTs) within the first four cycles. These DLTs were prolonged neutropenia (2), neutropenic fever (7), grade 4 thrombocytopenia (1), grade 4 dehydration (1), grade 3 infection (2), grade 3 oral mucositis (1) and pulmonary embolism (1).

Conclusions—Docetaxel 75 mg/m^2 IV, carboplatin AUC 6 IP administered on day 1, and paclitaxel 60 mg/m^2 IP administered on day 8, is the MTD when considering one cycle of treatment but was not feasible over four cycles due to bone marrow toxicity. We recommend reduction of carboplatin to AUC 5 should this regimen be considered for treatment in women with newly diagnosed advanced ovarian cancer.

Introduction

In 2011, approximately 21,880 new cases of ovarian cancer were expected to have been diagnosed in the U.S. with the vast majority having advanced stage disease requiring multi-agent chemotherapy containing platinum and taxane.[1] While these regimens have traditionally been given by intravenous infusion, several randomized trials have demonstrated improved progression-free and overall survival in patients treated with combination intravenous and intraperitoneal chemotherapy[2,3]. In a third landmark trial conducted by the Gynecologic Oncology Group (GOG-0172), patients were randomized to receive intravenous paclitaxel and cisplatin versus intravenous paclitaxel followed by intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8 for six cycles [4]. Median progression-free survival (PFS) was 18.3 months versus 23.8 months in favor of the IP arm (p=0.05). Median overall survival (OS) was 49.5 months versus 66.9 months in favor of the IP arm (p=0.03). These three studies prompted the publication of a National Cancer Institute Clinical Announcement recommending women be counseled regarding the clinical benefit associated with combined intravenous and intraperitoneal chemotherapy.[5] Despite this announcement, IP chemotherapy has not been widely accepted in the oncology community at large due to toxicity and difficulty with administration. Substituting carboplatin for cisplatin has been suggested as a possible way to decrease toxicity.[6,7,8]

Phase II trials have demonstrated that IP carboplatin produces objective responses in patients with small volume disease.[9,10] Intraperitoneal administration provides peak peritoneal fluid measurements 18-24 times higher than peak serum measurements.[9] As with IV administration, the dose-limiting toxicity is thrombocytopenia. While Markman reported evidence suggesting that IP cisplatin was superior to carboplatin prior to randomized trial data,[10] other authors suggest doses used in prior studies were too low, as the assumption of dose equivalency between carboplatin and cisplatin may have been erroneous.[11]

Docetaxel is a taxane with substantial activity against recurrent and primary ovarian cancer. Results from the SCOTROC trial comparing docetaxel at 75 mg/m^2 and paclitaxel at 175 mg/m^2 combined with carboplatin at AUC 5 showed similar PFS and OS in patients with ovarian cancer.[12] While docetaxel and carboplatin produced more myelotoxicity than paclitaxel and carboplatin, the combination of paclitaxel and carboplatin was significantly more neurotoxic.[12] Grade 2-4 sensory neurotoxicity was seen in 30% of patients on the paclitaxel arm vs. 11% on the docetaxel containing arm (P<0.001).[12] The persistent neuropathy seen with both IV paclitaxel/carboplatin, IV/IP paclitaxel/carboplatin and with IV/IP regimens containing paclitaxel and cisplatin is of concern.

Given the activity of docetaxel in this disease, this phase I study was performed to see whether docetaxel could be safely substituted for IV paclitaxel in regimens including IP platinum and whether its use would decrease persistent neuropathy. In this study (GOG 9916), we evaluated the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and the feasibility of incorporating intraperitoneal carboplatin with intravenous docetaxel and intraperitoneal paclitaxel in untreated patients with advanced ovarian, fallopian tube or peritoneal carcinoma.

Materials and Methods

Eligibility criteria

Patients with a histologic diagnosis of Stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, or ovarian carcinosarcoma, with optimal (≤ 1cm residual disease) or suboptimal disease following surgery were eligible. Patients with a GOG performance status of 0-2 were entered and treatment begun within 12 weeks of surgery. Laboratory criteria for eligibility included an absolute neutrophil count (ANC) ≥ 1,500/mcL, platelet count ≥ 100,000/mcL, white blood count ≥ 3,000/mcL, creatinine ≤ 1.5 times upper limit of normal (ULN), bilirubin ≤ 1.5 times ULN, alanine transaminase and aspartate transaminase ≤ 2.5 times ULN, and neuropathy (sensory and motor) ≤ grade 1 using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI CTCAE v3). This study was reviewed and approved by the Cancer Therapy Evaluation Program of the National Cancer Institute. All patients gave written informed consent before study entry in compliance with institutional, state, and federal regulations.

Treatment

On day 1, patients in all dose levels received docetaxel (55-75 mg/m^2) IV followed by carboplatin (AUC 5-6). Fixed dose intraperitoneal paclitaxel at 60 mg/m^2 was administered day 8 and each cycle was repeated every 21 days. Pretreatment steroids, histamine blocking agents and antiemetics were recommended. No growth factor support was allowed. The specific dosing levels are found in Table 1.

Port placement for intraperitoneal therapy was performed in accordance with GOG Surgical Procedures Manual. Intraperitoneal carboplatin or paclitaxel was reconstituted in 1 liter of warm normal saline and infused through the peritoneal catheter as rapidly as possible followed preferably by an additional liter of normal saline into the peritoneal cavity. Patients

were asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution.

Evaluation of toxicity

Patients underwent weekly laboratory evaluations and toxicity assessments. Toxicities were graded according to the NCI CTCAE v3. For both the dose escalation and feasibility phases, DLTs included: dose delay > two weeks due to failure to recover counts, febrile neutropenia, grade 4 neutropenia lasting > 7 days, grade 4 thrombocytopenia, clinically significant bleeding with grade 3 thrombocytopenia, study related grade 3 or 4 non- hematological toxicity (excluding fatigue, hypersensitivity reaction, hypokalemia, abdominal pain, nausea or vomiting) and any drug-related death. In addition, study treatment related neuropathy (Grade 2 or worse) persisting for two weeks was considered a DLT. Patients with intraperitoneal port-related complications were considered inevaluable for dose-limiting toxicity and replaced. Subsequent cycles of treatment did not begin until all toxicities were grade 1 or below; ANC was ≥1,500 cells/mcl; platelet count was ≥100,000 cells/mcl; creatinine was <2.0 mg%. Day 8 IP paclitaxel was not held due to low counts. Patients received therapy until disease progression, intolerable toxicity or completion of six cycles of therapy.

Statistical design

The first phase of this study, termed the dose escalation phase, identified the MTD using a standard 3+3 design.[13] Dose escalation for each cohort of three patients continued until a DLT was observed during the first cycle of therapy. If one patient out of three experienced a DLT, an additional three patients were enrolled at that dose level. The MTD was estimated by the maximum dose level at which ≤ 1 patient (among 6) experienced a DLT. No intra-patient dose escalation occurred. If a lower dose than the MTD was recommended, then this dose was simply called the recommended phase II dose (RPII Dose).

Following the dose escalation phase, the second phase of the study, called the feasibility phase began. This phase assessed treatment toxicities at the MTD over 4 cycles of therapy. The feasibility phase of the trial was carried out in a 2-stage group sequential design. The first stage required 20 patients. If four or fewer patients had adverse events, then the study closed early and the regimen was deemed feasible. If eight or more patients experienced adverse events, then the study closed and the regimen was declared not feasible. If 5-7 patients experienced adverse events, the study reopened to a second stage, targeting a cumulative accrual of 40 patients. If 11 or fewer patients had an adverse event, then the regimen was declared feasible. Otherwise, the regimen was declared not feasible.

If the true event rate for this regimen is 40%, the design provided a 90.6% chance of classifying the regimen as not feasible, with a 58.4% chance reaching this conclusion before beginning the second stage. If the event rate is 20%, the design provided a 91.2% chance of classifying the regimen as feasible and a 63.0% chance of reaching this conclusion before beginning the second stage.[14,15]

Results

Sixty-eight eligible patients were enrolled from August 2005 to June 2010. The mean patient age at enrollment was 59 years (range 34-81). Sixty-six patients had stage III disease while two had stage IV disease. Demographics are summarized in Table 2. Toxicity during the escalation phase is shown in Table 3.

In the dose escalation phase, three participants enrolled in Dose Level I receiving day 1 docetaxel at 55mg/m^2 IV and carboplatin IP at AUC 5 followed by day 8 IP paclitaxel. Two patients were unevaluable due to complications unrelated to protocol therapy. One patient had leakage of IP chemotherapy from the vagina and one expired due to pulmonary embolism. These patients were replaced and the remaining three evaluable patients had no dose-limiting toxicities.

As no patients had DLTs at Dose Level I, participants were enrolled at Dose Level II receiving docetaxel at 65 mg/m^2 IV and carboplatin IP at AUC 5 day 1. One patient experienced a surgical complication with a colo-vesical fistula. She was hospitalized after cycle 1 day 8 with grade 3 nausea vomiting, diarrhea, and dehydration. She developed hypotension and respiratory arrest and died of sepsis. Urine culture demonstrated Candida albicans while a tracheal aspirate showed streptococcus and staphylococcus. At the time of her fistula, she was febrile and pancytopenic, and this was considered a DLT. Therefore, the dose level was expanded to six patients. No other DLTs were seen in the other evaluable five patients. Three participants were then enrolled at Dose Level III receiving docetaxel at 75mg/m^2 IV and carboplatin IP at AUC 5 day 1. No DLTs were seen at this dose level and three participants were enrolled at Dose Level IV receiving docetaxel at 75mg/m^2 IV and carboplatin IP at AUC 6 day 1. One was unevaluable due to IP port complications. None of the remaining patients had DLTs during cycle 1.

Simultaneous to this trial, patients were enrolling in two other phase I trials within the GOG evaluating the safety of intravenous paclitaxel and intraperitoneal carboplatin. Those trials found the MTD of IP carboplatin to be an AUC of 6.[6,7] Therefore it was not felt realistic or safe to treat patients on this trial with an AUC of 7 and Dose Level IV was expanded for a total of eight patients. Two were unevaluable for dose-limiting toxicity due to port complications. None of the remaining 6 patients had a DLT during the first cycle. This dose level was the used for the feasibility phase.

Twenty-six patients were enrolled in the first stage of feasibility at Dose Level IV. Toxicity for the feasibility phase is shown in Table 4. Six patients were not evaluable due to hypersensitivity reaction (1), progressive disease (1), patient refusal (1) and surgical complications requiring reoperation (3). Twelve patients completed treatment without a DLT. In this first stage, initial review of the data revealed 7 DLTs, and the second stage of feasibility was opened. During the final patient data review at the time of writing this manuscript, an eighth DLT was discovered. These DLTs consisted of neutropenic fever (4), grade 4 thrombocytopenia (1), prolonged neutropenia (2), and grade 4 dehydration (1). The eighth DLT consisted of grade 4 ANC for >7 days with cycle 4.

Twenty additional patients were enrolled in the second stage of feasibility. Seven additional DLTs occurred for a total of 15 in the cohort of 40. These included grade 3 infection associated with IP port (2), grade 3 oral mucositis (1), neutropenic fever (3), and bilateral pulmonary emboli (1). The point estimate for the probability of a DLT is 37.5%, and the 90% CI for the probability of a patient experiencing a DLT within the first 4 cycles of therapy (adjusting the design to allow 8 DLTs instead of 7 in order to proceed to stage 2) is 37.5% and 23.5% - 51.0%.[16] When the twelfth DLT was identified, this regimen was deemed not feasible at this dose level and a memo was sent to all treating physicians. Options offered for patients who had not yet completed protocol therapy were removal from study or dose reduction of docetaxel, carboplatin or both at the discretion of the treating physician.

Discussion

Despite the publication of three adequately powered, positive randomized clinical trials and the NCI Clinical Announcement recommending, at a minimum, patients with advanced stage ovarian cancer (less than 1 cm. residual disease) be counseled about the benefits of regimens containing intravenous and intraperitoneal chemotherapy, this combination has not been widely accepted by the oncology community. Both the toxicity and the difficulty associated with administering intraperitoneal drugs appear to have slowed acceptance of this regimen. Various attempts have been made to optimize intraperitoneal chemotherapy regimens since 2006. These include omitting the day 8 IP paclitaxel, reducing the IP cisplatin dose to 75 mg/m^2, administering the IP cisplatin on day 1 rather than day 2, changing to 3 hour infusion of paclitaxel rather than 24 hour infusion and evaluating the role of using IP carboplatin rather than IP cisplatin. [6,7,8,17] Decreasing the cisplatin IP dose as well as substituting carboplatin IP have the potential to decrease the long-term neurotoxicity identified in GOG-0172. The use of docetaxel IV in this trial was hypothesized as another way of decreasing, if not avoiding, neurotoxicity associated with paclitaxel as well as providing an alternative for patients with hypersensitivity to paclitaxel.

Intravenous carboplatin AUC 6 and docetaxel 75mg/m^2 on day one and intraperitoneal paclitaxel 60 mg/m^2 on day 8 was the MTD of one cycle of treatment as defined in the dose escalation portion of this trial. However, these doses proved to have excess hematologic toxicity when administered over multiple cycles. While the statistical design would have allowed the study to be reopened for feasibility evaluation at a lower dose level of carboplatin AUC 5 in combination with docetaxel similar to the intravenous doses used in SCOTROC, decisions within the GOG to support IV/IP paclitaxel rather than docetaxel in the phase III setting made further exploration of the lower dose level unnecessary. [12] However, recent widespread shortages of paclitaxel as well as paclitaxel allergic reactions may necessitate the re-evaluation of docetaxel IV and carboplatin IP.[18] If substitution of paclitaxel for docetaxel in an IP regimen were planned, the toxicity seen in this regimen over multiple cycles would support using an AUC <6. Future statistical designs may utilize cycle 1 for the purposes of dose escalation, but the determination of the dose to use in the feasibility phase may incorporate results from the administration of 4 cycles in those patients in the escalation study, which may more accurately reflect the rates of DLTs. As was hypothesized, this regimen had less neuropathy than was seen in GOG-0172.

In conclusion, our results indicate that intravenous docetaxel at 75mg/m^2 and intraperitoneal carboplatin at AUC of 6 combined with intraperitoneal paclitaxel is not feasible over multiple cycles due to hematologic toxicity. Further study of the combination at an AUC <6 or with growth factor support may be indicated, especially given the on-going drug shortages with paclitaxel.

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Table 1

Schema of dosing levels

Dose Level	Drug	Dose (mg/m^2)	Drug	Dose	Drug	Dose (mg/m^2)
I	Docetaxel IV	55	Carboplatin IP	AUC 5	Paclitaxel IP	60
II	Docetaxel IV	65	Carboplatin IP	AUC 5	Paclitaxel IP	60
III	Docetaxel IV	75	Carboplatin IP	AUC 5	Paclitaxel IP	60
IV	Docetaxel IV	75	Carboplatin IP	AUC 6	Paclitaxel IP	60

IV- Intravenous
IP- Intraperitoneal
AUC- Area under the curve

Table 2

Demographics

Characteristic	Category	No.	%
Age	30-39	1	1.5
	40-49	11	16.2
	50-59	21	30.9
	60-69	24	35.3
	70-79	9	13.2
	80-89	2	2.9
Race	American Indian	4	5.9
	Hispanic	2	2.9
	Pacific Islander	1	1.5
	White	61	89.7
Site of Disease	Ovary	49	72.1
	Fallopian tube	3	4.4
	Peritoneal	16	23.6
Cell Type	Adenocarcinoma, Unsp.	3	4.4
	Clear Cell Carcinoma	2	2.9
	Endometrioid Adenocarcinoma	4	5.9
	Mixed Epithelial Carcinoma	7	10.3
	Serous Adenocarcinoma	52	76.5

Table 3

Dose escalation toxicity

Adverse event	**Dose level**															
	Level I				**Level II**					**Level III**				**Level IV**			
	N= 5				**N= 6**					**N= 3**				**N= 8**			
Grade of adverse event	1	2	3	4	1	2	3	4	5	1	2	3	4	1	2	3	4
Blood/bone marrow																	
Hemoglobin	2	1			5		1*			1	1			3	1		
White blood cells	2	1			2	2		1*					2		3	3	
Neutrophils			2		1	1		1*		2						5	
Platelets							1*										
Cardiac						1		1*							1		
Coagulation																	
Constitutional		3			3	1				2	1			4	1		
Dermatology	2				2					2	1			3			
Endocrine					2												
Gastrointestinal	2				2	2	1^	1*		1	2			4	1		
Genitourinary		1															
Hemorrhage																	
Hepatobiliary											1						
Infection	1					1			1*						1		
Metabolic	2	1			2	1	2@	1*						2	1		
Neurologic	1				2	1				2				1	1		
Ocular/visual	2									1							
Pain		1			1					1	1			3	1		
Pulmonary								1*							1		
Sexual		1															

Dose Level II:

* Colo-vesical fistula with pancytopenia, metabolic toxicity (hypocalcemia), hypotension, respiratory distress, and death occurring in a single patient.

Dose Level II:

^ Grade 3 Nausea and vomiting and

@ hypokalemia were not DLTs in this study.

Table 4

Toxicity in feasibility phase for four cycles (N= 40 patients)

Adverse event					
Grade of adverse event	0	1	2	3	4
Allergy	34	3	3	0	0
Auditory	37	0	3	0	0
Blood/bone marrow					
Hemoglobin	3	14	17	6	0
Neutrophils	0	1	1	4	34 +
Platelets	15	17	6	1	1*
Cardiac	37	2	1	0	0
Coagulation	39	1	0	0	0
Constitutional	6	17	16	1@	0
Dermatologic	5	16	19	0	0
Endocrine	36	3	1	0	0
Gastrointestinal	3	17	15	4@ £ †	1ˆ
Genitourinary	31	6	3	0	0
Hemorrhage	34	6	0	0	0
Hepatic	39	0	0	1#	0
Infection	20	0	11	9	0
Febrile Neutropenia	33	-	-	7@ # &	0
Infection with Grade 0 ANC	39	0	1	0	0
Infection with Grade 3 or 4 ANC	28	-	10	2<	0
Lymphatic	36	4	0	0	0
Metabolic	20	11	5	3 $	1&
Musculoskeletal	38	1	1	0	0
Neurologic	19	18	2	1ˆ	0
Ocular	31	6	3	0	0

Adverse event					
Pain	7	20	13	0	0
Pulmonary	30	7	3	0	0
Vascular	38	0	0	2[#] =	0

ANC- Absolute neutrophil count

Dose-limiting toxicities include:

[+] 2 patients with grade 4 neutropenia prolonged >7 days

[*] 1 patient with grade 4 thrombocytopenia

[@] 7 patients with neutropenic fever: Of these 7 patients with neutropenic fever, one patient also had grade 3 gastrointestinal/constitutional toxicity

[#] one also had grade 3 hepatic toxicity with prolonged LFT elevation /septic pelvic thrombophlebitis

[&] one also had grade 4 hyponatremia

[<] 2 patients with grade 3 port infections and grade 3 neutropenia

[=] 1 patient with pulmonary embolism

[£] 1 patient with grade 3 oral mucositis

[^] 1 patient with grade 4 dehydration

[†] Grade 3 nausea and vomiting

[$] Grade 3 metabolic (hypokalemia) were not DLTs in this study.