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PACLITAXEL POLIGLUMEX AND CARBOPLATIN AS FIRST-LINE THERAPY IN OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER: A PHASE I AND FEASIBILITY TRIAL OF THE GYNECOLOGIC ONCOLOGY GROUP

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Abstract

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest with the exception of Dr. Michael Bookman who has reported participation in the ad-hoc advisory board for Cell Therapeutics, Inc.

PRÉCIS

This study established a paclitaxel poliglumex dose of 135 mg/m^2 combined with carboplatin (AUC 6) as feasible for use in a phase III trial.

Purpose—To estimate the maximum tolerated dose (MTD) of paclitaxel poliglumex (PPX) in combination with carboplatin in patients with chemotherapy-naive ovarian, primary peritoneal or fallopian tube cancer, and to assess the feasibility of administering multiple cycles of this regimen.

Methods—The first 11 patients were treated in a standard 3+3 dose-seeking design, with carboplatin held constant at area under the curve (AUC) of 6 and PPX at 225, 175 or 135 mg/m^2. Pharmacokinetics of PPX and carboplatin were evaluated during this dose-seeking component of the trial. MTD was defined by acute dose-limiting toxicities (DLT) in the first cycle. Twenty additional evaluable patients were treated at the estimated MTD to assess the feasibility of this regimen over ≥ 4 cycles.

Results—PPX at 225 mg/m^2 resulted in DLT in 2/3 patients, and was de-escalated first to 175 mg/m^2 and then to 135 mg/m^2. PPX slowly hydrolyzed to paclitaxel and did not alter the pharmacokinetics of carboplatin. DLT within the first 4-cycles were observed in 3 patients (15%) treated at the MTD: neutropenia > 2 weeks (2), febrile neutropenia (1). Nineteen patients (95%) experienced grade 4 neutropenia. Sixteen patients (80%) had at least one episode of grade 3 thrombocytopenia. Three patients (15%) had grade 2 and one had grade 3 peripheral neuropathy. Complete response by CA-125 was 75%.

Conclusions—The recommended dose of PPX of 135 mg/m^2 with carboplatin (AUC=6) in newly diagnosed ovarian cancer was feasible for multiple cycles, but hematologic toxicity was greater compared with standard carboplatin and 3-hour paclitaxel.

Keywords

phase I trial; paclitaxel poliglumex; 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. A recent international consensus conference concluded that intravenous (IV) carboplatin and a 3-hour infusion of paclitaxel was the preferable regimen due to issues related to ease of administration, toxicity and quality of life, with no evidence of inferiority to other regimens.[1] In optimally debulked advanced ovarian cancer, there is evidence that the intraperitoneal administration of both cisplatin and paclitaxel may provide superior survival to standard therapy, but toxicity issues have prevented a consensus regarding the preferred regimen.[2]

Paclitaxel, one of the most active drugs in ovarian cancer, can cause serious hypersensitivity reactions, neutropenia and neurotoxicity. It also frequently causes total alopecia, which can have a significant adverse effect on body image.[3,4] In addition, paclitaxel is not water-soluble, requiring formulation in Cremophor EL® (polyoxylethylated castor oil) and ethanol. The Cremophor EL necessitates specific IV infusion sets and can itself be a cause of severe hypersensitivity reactions and hypotension. However, paclitaxel has also been reported to have a “platelet-sparing” effect on carboplatin-induced thrombocytopenia.[5]

Several approaches have been utilized to try to increase the therapeutic index of paclitaxel. These include liposomal encapsulation, nanoparticulate formulation and covalent linkage to macromolecule polymers that alter the pharmacokinetics of the parent drug.[6, 7, 8] Paclitaxel poliglumex (PPX, CT-2103, Xyotax®) is a water-soluble macromolecular conjugate that links paclitaxel to poly-L-glutamic acid.[9] This macromolecular drug conjugate eliminates the need for Cremophor and, therefore, decreases infusion time and the risk of hypersensitivity. Preclinical studies have demonstrated increased uptake and longer retention of PPX in tumors compared with unconjugated paclitaxel. In the bloodstream, PPX remains in its inactive,

conjugated form.[10, 11] PPX enters tumor cells by pinocytosis and the active drug is released by enzymatic action.

PPX has been studied in phase I and II trials alone and in combination with carboplatin or cisplatin in solid tumors, including ovarian cancer. When given as a single-agent, the maximum tolerated dose (MTD) was 235 mg/m^2.[12-15] A phase I trial demonstrated that PPX at 225 mg/m^2 and carboplatin at an area under the curve (AUC) of 6 had a manageable safety profile in patients with previously treated advanced solid tumors.[16]

We report the results of a multi-institutional phase I trial of PPX combined with a fixed carboplatin dose of AUC 6 in women with chemotherapy-naive ovarian, primary peritoneal or fallopian tube cancer. Recognizing that a phase I 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 PPX MTD given over multiple cycles.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients had to be ≥ 18 years of age and have previously-untreated, histologically-confirmed advanced stage, epithelial ovarian, primary peritoneal, or fallopian tube carcinoma with either optimal (≤1 cm residual disease) or suboptimal residual disease following surgery. Patients had to have a GOG Performance Status of ≤ 2 and been entered on study within 12-weeks postoperatively. Patients had to have adequate bone marrow function (absolute neutrophil count (ANC) ≥ 1,500/ul, platelets ≥ 100,000/ul), renal function (creatinine ≤ 1.5 × institutional upper limit normal (ULN)), hepatic function (bilirubin ≤ 1.5 × ULN, ALT, AST, and alkaline phosphatase ≤ 2.5 × ULN) and neurologic function (neuropathy, sensory and motor ≤ grade 1). Written informed consent consistent with all federal, state and local requirements was obtained from all patients before study entry.

Treatment Plan

On day 1 of each 21-day treatment cycle, PPX was administered as a 10 minute intravenous (IV) infusion, followed immediately by the IV administration of carboplatin over 30-minutes. Routine premedication to prevent hypersensitivity, nausea, or vomiting was not required. Patients could receive up to eight cycles of therapy. PPX was supplied by Cell Therapeutics, Inc. (Seattle, WA) in 20-ml vials containing 90 mg conjugated paclitaxel equivalent. Commercially available carboplatin (Paraplatin®, Bristol-Myers Squibb Oncology) was 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 and a baseline imaging study (computed tomography scan or magnetic resonance imaging of the abdomen and pelvis). Complete blood counts were performed weekly, and CA-125 testing, serum electrolytes, creatinine and liver function tests were obtained prior to each cycle. Patients were also examined prior to every course. Measurable lesions noted at baseline were reevaluated after cycles 4 and 8. Response Evaluation Criteria in Solid Tumors (RECIST)[17] and CA-125 levels[18] were used to assess response. Only patients in the feasibility phase were evaluated for response.

Dose-Limiting Toxicity

In accordance with the NCI Common Toxicity Criteria, Version 2 (NCI-CTC), 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 feasibility 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 ANC is $<1.0\times10^9$/L, Grade 4 neutropenia lasting ≥ 7 days and Grade 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 (Table 1). Subsequent cycles of therapy could not begin until the ANC was ≥ 1,500 cells/uL (NCI-CTC Grade 1) and the platelet count ≥ 75,000 cells/uL. Therapy could be delayed for a maximum of 2 weeks until these values were achieved. Two dose reductions of PPX were allowed for febrile neutropenia and/or grade 4 neutropenia lasting ≥ 7 days. Also, patients with grade 3 thrombocytopenia, or thrombocytopenia-associated bleeding that required a platelet transfusion, could have a one-time dose reduction of carboplatin. A second occurrence of grade 3 thrombocytopenia required a dose reduction of PPX. 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 not allowed.

Dose modification was required for any drug-related grade 3 or 4 non-hematologic toxicity. Treatment was discontinued in patients with persistent peripheral neuropathy ≥ grade 3. Patients with non-hematologic toxicity had to return to ≤ grade 1 before continuing therapy.

Pharmacokinetic Assessment

On days of pharmacokinetic evaluation, carboplatin was administered one hour after the PPX infusion. Up to 28 serial plasma specimens, 17 ultrafiltrate plasma specimens, and seven urine specimens were collected from each patient participating in the dose-seeking phase of the trial. Heparinized-blood was drawn during cycles 1 and 4 immediately before the 10-minute PPX infusion, at 20, 40 and 90 min, 3, 4, 6, 8, 12, 24, 36,and 48 hours after the start of PPX infusion, on days 8 and 15 during cycle 1, and before starting cycles 2 and 3. Plasma was prepared by centrifuging the blood at 2,000 × gravity for 15 minutes. Plasma ultrafiltrates were prepared from heparinized-blood drawn during cycles 1 and 4 immediately before carboplatin administration, 30 minutes after the start of the 30 minutes infusion and again 2, 3, 5, 7, 11, 23 and 35 hours post-infusion start by centrifuging the plasma through an Amicon Centrifree® YM-30 centrifugal filter device (Millipore Corporation, Bedford, MA). Total urine volume produced during six 4-hour time intervals and one 24-hour time interval, for a total of 48 hours during the first cycle, was collected commencing at the time of PPX administration. All specimens were stored at −70°C until testing

The concentrations of conjugated taxanes and unconjugated paclitaxel in the serial plasma specimens were determined by liquid chromatography-tandem mass spectrometry validated methods by Tandem Labs Salt Lake City, Utah. The quantification of carboplatin in plasma ultrafiltrate was performed by HPLC combined with inductively coupled plasma mass spectrometry by Elemental Research Inc, North Vancouver, British Columbia, Canada. Non-compartmental pharmacokinetic analyses were performed on the temporal profiles of conjugated taxanes and unconjugated paclitaxel in plasma and urine, and of carboplatin in plasma ultrafiltrate and urine using WinNonlin Enterprise ver 4.1software (Pharsight Corporation, Mountain View, CA).

Statistical Considerations

The study was carried out in two phases. The dose-seeking phase was designed to find the MTD of the study regimen. Once an estimate of the MTD was established, the second "feasibility" phase was initiated. The purpose of the feasibility phase was to obtain more precise estimates of the toxicity of the study regimen, to be assured that the recommended dose from the escalation phase was not too toxic for incorporation into a phase III trial.

A two-stage sequential design was used 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 2. Based on the estimated frequency of dose modification and/or delay with the two-drug combination of carboplatin and paclitaxel in Protocol GOG-158, 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 $\geq 40\%$[19]. 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

Thirty-two patients were entered on the trial, including 11 in the dose-seeking phase and 21 in the feasibility phase. One patient in the feasibility phase suffered a stroke shortly after the first cycle and was not considered evaluable. Demographics are listed in Table 3.

Adverse Events

Two of the first three patients at a PPX dose of 225 mg/m^2 experienced a DLT with the first cycle (neutropenic fever and grade 4 neutropenia > 7 days). Because of this, the planned dose escalation was amended to an escalating/de-escalating scheme starting at 175 mg/m^2 (Table 4). Two of five patients treated at a PPX dose of 175 mg/m^2 experienced a first cycle DLT (failure to recover counts in 2 weeks and grade 4 neutropenia > 7 days). There were no DLTs observed in the 3 patients treated with a dose of 135 mg/m^2. Therefore, this dose was chosen for the feasibility phase.

Three of 20 evaluable patients in the feasibility phase experienced a DLT within the first 4 cycles (febrile neutropenia with failure to recover counts in 2 weeks, and two failures to recover counts in 2 weeks). Therefore, this dose was considered feasible over multiple cycles. Sixteen patients (80%) completed 6 cycles, and 11 (55%) completed 8 cycles. Myelotoxicity was considerable with 19 patients (95%) experiencing at least one episode of grade 4 neutropenia, and 16 patients (80%) experiencing at least one episode of grade 3 thrombocytopenia. Twelve patients (60%) had grade 3 thrombocytopenia before cycle 6. Three patients (15%) had grade 2 and one patient had grade 3 peripheral neuropathy (Table 5).

Pharmacokinetics of Paclitaxel Poliglumex

The pharmacokinetics of PPX were evaluated in serial plasma specimens from all 11 patients in the dose-seeking phase after cycle 1 and eight of those patients after cycle 4 (Table 6). The concentration of conjugated taxanes in plasma declined in a bi-exponential manner after the end of the first PPX infusion. The distribution phase lasted up to 48 hours after PPX infusion when the apparent terminal elimination phase began. The elimination phase was slow with measurable conjugated taxanes detected 8 days after PPX infusion in all 11 patients, and 15 days after PPX infusion in two of five patients treated with 135 mg/m^2, three of five patients treated with 175 mg/m^2, and all three patients treated with 225 mg/m^2. Conjugated taxanes

were not detected in the eight patients with a pre-cycle 2 plasma specimen or the seven patients with a pre-cycle 3 plasma specimen. The observed systemic plasma clearance (CL) of PPX after cycle 1 was low and associated with a long apparent terminal half-life ($t_{1/2,z}$). Neither CL nor $t_{1/2,z}$ varied systematically across the three PPX doses. The mean volume of distribution in the post-distribution phase (Vz) during the first cycle of PPX was approximately 4-10 times greater than the volume of distribution at steady-state (Vss). Unconjugated paclitaxel, was slowly released from the polymeric backbone and accounted for <1%, on average, of the conjugated taxane AUC during cycles 1 and 4. During cycle 1, the estimated $t_{1/2,z}$ for unconjugated paclitaxel was approximately 3-4 times lower than that of conjugated taxane. The pharmacokinetic parameters for unconjugated paclitaxel between cycle 1 and cycle 4 did not change substantially. Two days after the first PPX administration, approximately 6% of the PPX dose was excreted in the urine as conjugated taxanes and <2% of the dose was excreted as unconjugated paclitaxel. Mean renal clearance (CL_R) of the conjugated taxanes was about 15 times lower than the mean CL.

Pharmacokinetics of Carboplatin

The pharmacokinetics of carboplatin were examined in 11 patients during cycle 1 and in 8 patients during cycle 4 (Table 6). The administered dose ranged from 330 to 822 mg during cycle 1 and from 330 to 780 mg during cycle 4, corresponding to 6.18 +/−1.16 and 5.12 +/− 1.18 mg/ml*min, respectively, and demonstrating the precision of achieving an AUC of 6 mg/ml*min of carboplatin. Plasma carboplatin concentrations declined mono-exponentially with a $t_{1/2,z}$ of approximately 3 hours. The free fraction of carboplatin was efficiently eliminated from the plasma compartment. Similar pharmacokinetic parameters were observed during cycle 4. In addition, the average temporal profiles of carboplatin during cycle 1 and cycle 4 were super-imposable (data not shown), indicating that the pharmacokinetics of carboplatin when given in combination with PPX was not time-dependent. Carboplatin was not detected in any of the eight patients with pre-cycle 2 plasma or the seven patients with pre-cycle 3 plasma. Approximately 60% of the carboplatin dose was excreted in urine during first seven hours after the carboplatin infusion. By 48 hours after the start of cycle 1, about 64% of the carboplatin dose had been excreted in urine.

Response

Only 10 of the 20 patients in the feasibility phase had measurable disease. There was 1 complete response and 3 partial responses (40% response rate). Of the sixteen patients evaluable for CA-125 response, complete and partial response rates were 75% and 25%, respectively.

DISCUSSION

Conjugating active cytotoxic agents to water-soluble macromolecular carriers such as polyamino acids is an attractive approach to minimize toxicity and increase efficacy. Based on prior experience with the combination of PPX and carboplatin in pretreated patients it was expected that a PPX dose of 225 mg/m^2 was a reasonable starting point for a phase I evaluation of this combination in untreated patients.[16] However, this dose was associated with excessive first-cycle hematologic toxicity necessitating de-escalation to 175 mg/m^2 and then 135 mg/m^2. When given at 135 mg/m^2 over multiple cycles, myelotoxicity was still significant. In the feasibility phase, 95% grade 4 neutropenia and 80% grade 3 thrombocytopenia was observed. In GOG-158, 72% grade 4 neutropenia and 39% grade 3 and 4 thrombocytopenia was observed with paclitaxel (175 mg/m^2) and carboplatin (AUC=7.5).[19] Prolonged infusions of paclitaxel are known to be more myelosuppressive than short infusions, and the slow release of paclitaxel from PPX may cause the drug to act more like a prolonged infusion on the bone marrow and diminish the platelet-sparing effect associated with paclitaxel.[5] Neurologic toxicity was similar to that seen in GOG-158.

Pharmacokinetic analysis demonstrated that PPX was stable in the systemic circulation with limited release of free paclitaxel in the plasma compartment. The volume of distribution of conjugated taxanes increased during the terminal disposition phase, which is consistent with slow intracellular PPX uptake in tissues with hyper-permeable vasculature such as tumor tissue. The limited renal elimination efficiency of unconjugated paclitaxel following a 10-min infusion of PPX is consistent with the data reported for paclitaxel, and excretion in bile and metabolism are likely to account for most of the elimination of PPX.[20,21] Co-administration with PPX did not alter the pharmacokinetics of carboplatin because the pharmacokinetic parameters observed for carboplatin are in keeping with those reported in the literature for carboplatin administered as a single agent[22, 23] or in combination with paclitaxel.[24, 25]

This phase I trial established an MTD of PPX at 135 mg/m^2 when given every 3 weeks with carboplatin at an AUC of 6 in women with untreated advanced ovarian, fallopian tube or primary peritoneal cancer. An expanded, feasibility phase demonstrated that the PPX MTD of 135 mg/m^2 was tolerable over multiple cycles, but had a greater than expected incidence of granulocytopenia and thrombocytopenia compared to standard carboplatin and paclitaxel regimens. PPX metabolism to unconjugated paclitaxel is at least partially dependent on cathepsin B.[26] In that cathepsin B activity can be induced by estrogen, it is possible that toxicity and efficacy of PPX may vary in studies with different proportions of men and women.[27] This, along with additional definitions of DLT in our study (grade 4 neutropenia $\geq$ 7 days, failure to recover counts in 2 weeks) may have resulted in the lower MTD than previously reported.[16] The number of patients with measurable disease (N=10) in this study was too low to make a meaningful statement regarding response rate; however, the high complete response rate by CA-125 criteria is what would be expected from front-line therapy using a platinum and taxane combination in this disease.

Although the combination of PPX and carboplatin seems to be more myelotoxic than carboplatin and paclitaxel, serious outcomes associated with myelosuppression, such as febrile neutropenia or bleeding, were infrequent. The 5% incidence of febrile neutropenia would not make criteria for the use of prophylactic colony stimulating factors based on current American Society of Clinical Oncology guidelines.[28] Advantages of the PPX and carboplatin combination include less alopecia, much shorter infusion times, and minimal hypersensitivity in untreated patients despite no premedication with steroids or antihistamines. Efficacy regarding response and survival compared to carboplatin and paclitaxel will require a randomized controlled trial. Currently, the GOG is conducting a randomized maintenance trial of paclitaxel poliglumex versus paclitaxel, each given on a 28 day schedule in advanced ovarian cancer. If paclitaxel poliglumex is found to be superior to paclitaxel there would be further justification for testing this regimen in a front-line setting.

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Table 1

Dose modifications

Study Drug	Dose Level	2 Level Reduction	1 Level Reduction	Initial Starting Dose
Paclitaxel	−1	80 mg/m^2	100 mg/m^2	135 mg/m^2
Poliglumex	1	100 mg/m^2	135 mg/m^2	175 mg/m^2
	2	135 mg/m^2	175 mg/m^2	225 mg/m^2
Carboplatin	Any		AUC 4.5	AUC 6

AUC = area under the curve

Table 2

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 3

Demographics.

Characteristic	Category	No. of Cases	% of Case
Age (years)	40-49 years	7	22.6
	50-59 years	9	29.0
	60-69 years	9	29.0
	70-79 years	5	16.1
	80-89 years	1	3.2
Ethnicity	Hispanic	2	6.5
	White	29	93.5
Performance Status	0	21	67.7
	1	10	32.3
Site of Disease	Ovary	27	87.1
	Fallopian tube	1	3.2
	Primary Peritoneal	3	9.7
Cell Type	Adenocarcinoma, Unspecified	1	3.2
	Endometrioid Adenocarcinoma	2	6.5
	Mixed Epithelial Carcinoma	6	19.4
	Transitional Cell Carcinoma	1	3.2
	Serous Adenocarcinoma	21	67.7
Grade	1: Well differentiated	1	3.2
	2: Moderately differentiated	2	6.5
	3: Poorly differentiated	25	80.6
	Not graded	1	3.2
	Not submitted	2	6.5

Table 4

Escalation, de-escalation schema

Dose Level	PPX mg/m^2	Up to # of patients	Next group of patients depend on # with DLT at current dose			When 2 DLTs have occurred
			If 0 DLT	If 1 DLT	If 2 DLTs	
−1a	135	3	Stop, Go to expanded phase	Go to −1b	Stop	Stop, no feasibility phase
−1b	135	3	Stop, Go to expanded phase	Stop	n/a	Stop, no feasibility phase
1a	175	3	Go to 2a	Go to 1b	Stop	Go to −1
1b	175	3	Go to 2a	Stop	n/a	Go to −1
2a	210	3	Stop, Go to expanded phase	Go to 2b	Stop	Stop, Go to 1,feasibility phase
2b	210	3	Stop, Go to expanded phase	Stop	n/a	Stop, Go to 1, feasibility phase

n/a = not applicable

Table 5

Toxicity in feasibility phase

Adverse Effect	Grade 0	1	2	3	4	Total
Leukopenia	1	0	7	11	1	20
Thrombocytopenia	1	2	1	16	0	20
Neutropenia	0	0	0	1	19	20
Anemia	0	3	14	3	0	20
Allergy	19	1	0	0	0	20
Cardiovascular	17	2	0	1	0	20
Constitutional	3	14	2	1	0	20
Dermatologic	8	7	4	1	0	20
Gastrointestinal	3	8	8	1	0	20
Genitourinary/Renal	19	1	0	0	0	20
Hemorrhage	18	1	0	1	0	20
Hepatic	11	8	1	0	0	20
Infection	19	0	0	1	0	20
Metabolic	11	5	2	2	0	20
Neuropathy-sensory	5	11	3	1	0	20

Table 6

Summary of the pharmacokinetic parameters for conjugated taxanes, unconjugated paclitaxel and carboplatin after cycle 1 and cycle 4 administration of CT-2103 at 135 mg/m^2, 175 mg/m^2 or 225 mg/m^2 and carboplatin (AUC 6)

Drug	**Conjugated Taxanes (mg/m^2)**						**Unconjugated Paclitaxel (mg/m^2)**						**Carboplatin**	
Cycle	**1**			**4**			**1**			**4**			**1**	**4**
Dose	**135**	**175**	**225**	**135**	**175**	**225**	**135**	**175**	**225**	**135**	**175**	**225**	*****	*****
Cases	**3**	**5**	**3**	**5**	**2**	**1**	**3**	**5**	**3**	**4**	**2**	**1**	**11**	**8**
C_{max}														
mean	87.0	84.7	130.7	65.4	85.2	104.0	0.32	0.42	0.47	0.29	0.29	0.50	42.4	33.3
SD	11.5	13.2	25.7	4.6	29.4		0.18	0.21	0.14	0.05	0.04		8.93	11.1
AUC														
mean	953	1006	2216	901	1455	1995	4.07	5.18	7.19	4.16	4.05	8.79	103	85.3
SD	361	229	588	139	846		1.09	3.19	0.76	0.35	1.62		19.4	19.7
CL														
mean	154	180	107	153	145	113							6.50	7.12
SD	50	37	33	25	84								1.60	2.21
$t_{½,z}$														
mean	89.2	55.3	57.7	6.75	9.05	11.3	25.7	16.1	13.4	13.9	15.2	13.9	3.16	2.88
SD	58.9	21.5	12.3	1.33	3.14		9.01	3.97	1.86	2.21	0.07		0.98	0.63
V_z														
mean	21.6	14.5	9.25	1.47	1.70	1.83							29.3	28.5
SD	19.7	7.60	4.65	0.23	0.45								10.6	7.09
V_{ss}														
mean	2.66	2.79	2.06	1.81	1.94	1.92							16.1	18.0
SD	1.86	0.82	0.40	0.12	0.62								3.53	4.76
fe°														
mean	6.01	6.40	5.83				1.27	1.97	1.80				64.0	
SD	1.67	1.89	0.85				0.22	0.51	0.21				14.1	
CL_R														
mean	9.18	12.5	7.31				508	884	622					
SD	0.79	5.39	2.89				112	403	94.6					