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ORIGINAL ARTICLE

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Phase I study of the novel taxane CT-2103 in patients with advanced solid tumors

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Abstract *Background*: CT-2103 (Cell Therapeutics, Seattle, Wash.) is a water-soluble macromolecular conjugate of paclitaxel to a polyglutamate backbone, designed to enhance tumor permeability and to improve intratumoral delivery of paclitaxel. Preclinical studies indicate that CT-2103 has substantial antitumor efficacy in xenograft tumor models. *Methods*: We performed a phase I trial in patients with advanced solid tumors to determine the maximum tolerated doses (MTD) of CT-2103 when administered as short intravenous infusion every 3 weeks. *Results*: Seven patients received a total of 16 cycles (range 1–3) of CT-2103 at doses of 235 and 270 mg/m^2. Two of five patients treated at 235 mg/m^2 and one of two patients treated at 270 mg/m^2 experienced grade 3/4 neutropenia. Four patients experienced a marked increase in PTT within 30 min of the start of infusion. Neuropathy was more severe than expected. Two patients developed grade 3 neuropathy that prompted a 50% dose reduction of CT-2103 and persisted for 8 months in one, and over a year in the other. Three patients experienced grade 1 or 2 neuropathy. Neurotoxicity was cumulative and prevented patients from receiving prolonged administration of CT-2103. *Conclusions*: The unexpectedly high rate of cumulative toxicity observed in our study needs to be taken into consideration in future trials of CT-2103. Prior taxane use may not be a predictor of severe neurotoxicity.

Keywords CT-2103 · Phase I · Taxanes · Neurotoxicity

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Introduction

The striking clinical efficacy of paclitaxel is achieved at the cost of some untoward effects, including hypersensitivity reactions, neutropenia and cumulative neurotoxicity [1–3]. In addition, the formulation required to render the drug soluble contains Cremophor, and so prolonged administration schedules are required. Cremophor EL itself is biologically and pharmacologically active and has a significant impact on the pharmacokinetics of paclitaxel [4, 5]. Studies in animals have shown that Cremophor can induce histamine release and hypotension within 10 min of administration [3, 6, 7]. Additionally, Cremophor had been considered the causal agent of hypersensitivity reactions reported with other drugs formulated with Cremophor EL, such as cyclosporine [3, 8]. For these reasons, much attention has been paid to modifying the formulation of paclitaxel to identify equally or more active preparations, while ameliorating toxicity. One approach to improving the formulation of paclitaxel, and to modulate its distribution and elimination in the body, is to conjugate paclitaxel molecules to a macromolecular carrier. Polyamino acids such as polyglutamate have several potential advantages as carrier molecules, including a high proportional loading of drug, and ease of catabolism by intracellular lysosomal enzymes to release free drug.

CT-2103 (poly(L)glutamate–paclitaxel) is a water-soluble macromolecular preparation of conjugated paclitaxel designed to exploit some of these potential advantages [9–12]. It has been reported to enhance tumor permeability of the drug, to prolong intratumoral retention, and so to result in improved delivery of paclitaxel to the tumor. The preparation may also minimize the toxicity of paclitaxel to normal organs. It comprises paclitaxel covalently linked at the 2′-hydroxyl groups through an ester bond to poly-L-glutamate to form a macromolecular drug delivery system. The CT-2103

enters cells by pinocytosis and concentrates in lysosomes, where cleavage of the covalently bound paclitaxel is assumed to take place. Preclinical studies have indicated that CT-2103 may enhance the therapeutic index for paclitaxel in humans. Indeed, CT-2103 has a higher maximum tolerated dose (MTD) than paclitaxel and an increased antitumor efficacy in xenogeneic tumor models when paclitaxel-equivalent MTD doses are compared to unconjugated paclitaxel MTD doses [13, 14]. Phase I and II clinical studies have been conducted using doses of CT-2103 ranging from 175 to 270 mg/m^2 either as a single agent or in combination with conventional chemotherapy [15–21]. The enhanced aqueous solubility and lack of Cremophor results in a convenient infusion time of 10–20 min. The most frequent adverse events reported are neutropenia and neuropathy.

We conducted a phase I study of escalating doses of CT-2103 in patients with previously treated solid malignancies. The starting dose of 235 mg/m^2 represented an escalation and dose intensification of the drug over levels that had been tolerable in concurrent trials.

Patients and methods

Eligibility

Eligible patients were at least 18 years of age with histologically confirmed solid tumors that were refractory to standard therapy or for which no effective therapy was available. An ECOG performance status of 0 or 1 and a life expectancy ≥16 weeks were required. Patients had adequate bone marrow (neutrophils ≥1500 mm^{-3} and platelets ≥100,000 mm^{-3}), renal (serum creatinine not more than 1.5 times the upper limit of normal) and hepatic (serum bilirubin not more than 1.5 times the upper limit of normal, and AST/ALT not more than 2.5 times the upper limit of normal) function. All patients had recovered from prior treatment and had received no chemotherapy, immunotherapy, or radiotherapy in the previous 4 weeks (6 weeks for nitrosoureas and mitomycin C). The exclusion criteria included: no treatment with more than two regimens containing an alkylating agent with stem cell toxicity (melphalan, nitrosourea, busulfan, mitomycin C, and carboplatin); no preexisting neurotoxicity from previous treatment equal to or greater than National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 2; no active brain metastasis; and no serious uncontrolled medical disorder or active infection that would impair the ability of the patient to receive the study treatment. Because of excessive neurotoxicity, beginning with patient 7, exclusion criteria were subsequently modified to: no more than four cycles of a neurotoxic agent (taxane, vinca alkaloid, epothilone, platinum, or any experimental agent with neurotoxicity as a known side effect); and no preexisting neurotoxicity from previous treatment greater than NCI-CTC grade 1. The study was approved by the institutional review board of the University of Pennsylvania. All patients received information on the purpose and conduct of this study, and signed written informed consent.

Pretreatment evaluation and follow-up

Pretreatment evaluation consisted of a history and physical examination, full blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), serum electrolytes, creatinine and liver function tests, urinalysis, electrocardiogram, baseline imaging study, and assessment of ECOG performance status. Hematologic evaluations including blood counts, PT, aPTT and biochemical profiles were performed weekly during the first two cycles, and during the third week of every cycle thereafter. Since during the conduct of this study we identified abnormal coagulation parameters (PT, aPTT) in patients receiving CT-2103 concomitantly with warfarin, beginning with patients 5 and 6, frequent blood samples for PT and aPTT analysis were obtained on day 1 of treatment. Patients were examined prior to every course. Lesions noted at baseline that were measured or evaluated by radiographic scan or X-ray were reviewed before every other course and evaluated for response according to standard criteria [22]. Patients exhibiting response to the treatment or stable disease continued on therapy until progression.

Study design and drug administration

The purpose of this trial was to determine the MTD, toxicity, and efficacy of escalating doses of CT-2103 administered once every 3 weeks to patients with advanced tumors. CT-2103 for intravenous injection (IV) was supplied by Cell Therapeutics (Seattle, Wash.) as a white to off-white lyophilized cake in a 20-ml clear glass vial containing CT-2103 90 mg paclitaxel-equivalent (all doses of the polymer are expressed in these units for consistency). The CT-2103 solution was obtained by adding 10 ml water-for-injection to the lyophilized cake to a final concentration of 9 mg/ml. The calculated dose for each patient was diluted with 100 ml 5% dextrose in water (D5W) and kept in a non-polyvinyl infusion bag. The CT-2103 was administered as an IV infusion over 10–20 min every 3 weeks. The starting dose was 235 mg/m^2 paclitaxel-equivalent.

Evaluation

Toxicity during each treatment cycle was assigned according to the NCI Common Toxicity Criteria, version 2.0 (Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Md.). The dose was increased in groups of three new patients provided that patients treated at the next lower dose level did not experience dose-limiting toxicity (DLT). If DLT

occurred during the first cycle of treatment in any patient, an additional three patients were treated at that dose level. The MTD was defined as one dose level below the dose that induced DLT in greater than one-third of patients. A maximum of 12 patients were to be evaluated at the MTD. Doses were not escalated within patients. The DLT was defined as (1) grade 4 neutropenia lasting >7 days, (2) febrile neutropenia defined as fever (temperature ≥38.6°C) of unknown origin while the absolute neutrophil count (ANC) was <1000 mm^{-3}, (3) platelet count $<25{,}000$ mm^{-3}, (4) any nonhematologic toxicity related to study treatment of grade 3 or more, except nausea, vomiting, and diarrhea unless maximally treated with appropriate medical management, or (4) any drug-related death. Hypersensitivity reactions were not considered DLTs. Patients did not receive prophylactic medications for hypersensitivity prior to the administration of CT-2103, unless there was a history of hypersensitivity to paclitaxel. Use of granulocyte-colony stimulating factor (G-CSF) or granulocyte-monocyte-colony stimulating factor (GM-CSF) was not permitted during cycle one of the study. Response was defined according to RECIST [22].

Table 1 Patient characteristics

No. of patients	
Entered	7
Assessable	7
Gender	
Male	3
Female	4
Age (years)	
Range	76–56
Median	62
ECOG performance status	
1	3
0	4
Tumor type	
Melanoma	1
Ovary	2
Pancreas	2
Lung (small-cell)	1
Bladder	1
Prior therapy	
Chemotherapy	6
Sargramostim	1
Radiotherapy	2
Prior taxanes	5
Grade 1 neuropathy at baseline	2
History of diabetes mellitus	2

Results

Patient characteristics

A total of seven patients (four females and three males) with a range of solid tumor diagnoses and good performance status received a total of 16 cycles (range 1–3) of CT-2103 at doses of 235 mg/m^2 (five patients) and 270 mg/m^2 (two patients). The demographic characteristics of the patients are presented in Table 1. Six patients had been previously treated with chemotherapy, including five patients who had received taxane-based therapy, one patient with melanoma who had been treated only with sargramostim, and two patients who had received radiation therapy. Two patients, one each with ovarian and pancreatic cancer, had grade 1 residual neuropathy from their previous treatment with taxane-based chemotherapy. These patients had received 12 and 13 cycles of taxanes in the past. All patients were evaluable for response and toxicity.

Hematologic toxicity

Neutropenia, was the most prominent hematologic toxicity (Table 2). Five patients were treated at the dose of 235 mg/m^2. Two of these patients developed grade 4 neutropenia, which lasted for 5 days in one of them. Neutropenia was not a DLT and the CT-2103 dose was reduced by 25% in the second cycle. Two patients developed grade 2 neutropenia. Two patients were treated at the second dose level of 270 mg/m^2 and one developed grade 3 neutropenia. There were no episodes of febrile neutropenia, no delays in the administration of the subsequent cycles and the toxicity was not cumulative. None of the patients developed thrombocytopenia. Since during the conduct of this study we observed abnormal coagulation parameters (PT and aPTT) in patients receiving CT-2103 concomitantly with warfarin, frequent assessments of PT and aPTT on all subsequent patients were performed on days 1 and 2 of the first cycle of therapy. Four patients experienced a dramatic increase in aPTT (more than twice the upper normal limit) within 30 min of the start of infusion. The aPTT returned to a normal value between 24 and 48 h in all patients and none experienced bleeding episodes. Addition of CT-2103 to normal plasma in vitro resulted in a dose-dependent increase in aPTT and PT with effects seen at concentrations above 16 mg/ml. The effect was not neutralized by the addition of hexagonal phase phospholipids. The findings are most consistent with a non-specific interfering substance in the assay. These results will be discussed in more detail in a manuscript in preparation.

Nonhematologic toxicity

The most important non-hematologic toxicity was neuropathy (Table 2). Peripheral sensory neuropathy occurred in five of the patients, and was not clearly related to dose level. The time-course and dose-relationship of the neuropathy are shown schematically in Fig. 1. Two patients, both treated with two prior taxanes, both with grade 1 neuropathy at the beginning of treatment, tolerated the first cycles (one and two, respectively) of CT-2103 without worsening of their toxicity. However, with the next dose, they both had worsening to grade 3 toxicity. In accordance with the protocol, reduced doses

Table 2 Grade 2 or greater toxicity by dose level, presented as the number of patients with each toxicity grade

CT-2103 dose (mg/m^2)	No.	Grade																	
		Neutropenia			Thrombocytopenia			Nausea or vomiting			Fatigue			Neuropathy			↑ PTT		
		2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
235	5	2	0	2	0	0	0	0	0	0	3	0	0	1	2	0	0	2	0
270	2	0	1	0	0	0	0	0	0	0	2	0	0	1	0	0	0	2	0

were given with the next cycle, but the neuropathy worsened further, with pain in the extremities as a major manifestation, though the grade did not change. Of the remaining five patients, two experienced grade 2, one grade 1 and two no neurotoxicity after the periods indicated in Fig. 1. One of the patients with grade 2 had treatment discontinued in light of the toxicity, while the other progressed at this stage.

One of the patients with grade 3 toxicity was a 58-year-old woman with ovarian cancer who had grade 1 residual peripheral neuropathy at the time of beginning CT-2103. Her neuropathy worsened to grade 3 after three cycles, and had not resolved at the time of her death from progressive disease 8 months later. The second patient was a 52-year-old male with pancreatic cancer who had failed multiple chemotherapy regimens. He also had grade 1 neuropathy at the beginning of CT-2103 treatment. His neuropathy persisted for more than 1 year, and required intensive treatment with gabapentin and carbamazepine. The patients with grade toxicity had this side effect persist for more than 2 months.

Other non-hematologic toxicities were mild and included grade 1 or 2 nausea, fatigue and arthralgia/myalgia, all typical in onset and severity for a taxane (Table 2). One of the potential advantages with the formulation of the taxane in this polymer is the ability to administer the drug rapidly: no hypersensitivity or other acute reactions were observed.

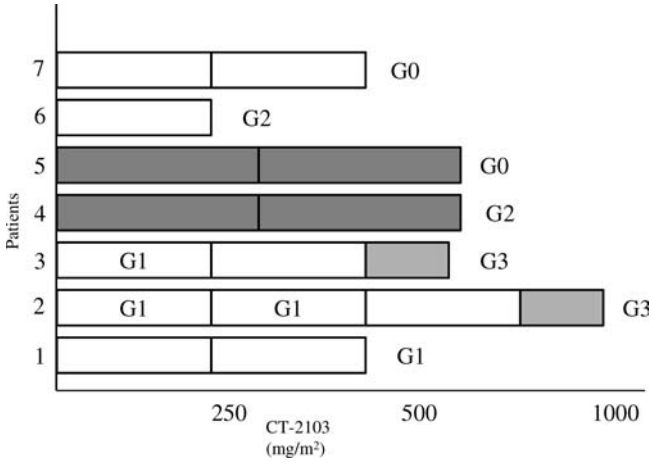

Fig. 1 Time-course and dose-relationship of the neuropathy. *Bars* represent the individual patients and the number of cycles and the dose of CT-2103 (mg/m^2) received by each patient is shown in the *horizontal axis*. *Dark gray* bars represent the two patients who received CT-2103 at the dose of 270 mg/m^2. *Light gray* areas indicate a 50% dose reduction. Patients 2 and 3 had persistent neuropathy 8 months and 1 year after discontinuation of CT-2103, respectively

Response

In this study we did not observe any partial or complete response. Both patients with grade 3 neuropathy achieved disease stabilization, but had to be removed from the study because of the neurotoxicity.

Discussion

We conducted a phase I clinical trial in patients with advanced solid tumors to determine the MTD of CT-2103 when administered as short IV infusion every 3 weeks. We were able to administer CT-2103 at two dose levels only, 235 and 270 mg/m^2. Neutropenia and peripheral sensory neuropathy were the major toxicities observed. Two of five patients treated at the dose of 235 mg/m^2 and one of the two patients treated at 270 mg/m^2 experienced grade 3 or 4 neutropenia in the first cycle. The duration of the neutropenia was short, not cumulative and not dose-limiting. There were no delays in treatment because of neutropenia. This degree of neutropenia is not strikingly different from what one would expect with paclitaxel alone at these doses.

Neuropathy was more severe than expected, however. Five of the seven patients developed neuropathy (four of them treated at 235 mg/m^2); the toxicity was severe in two of them and persisted for 8 months in one, and over a year in the other. Both of these had had prior treatment with taxanes, and both had received a single additional dose of CT-2103 in the face of existing neurotoxicity. Clearly one can recommend that patients have CT-2103 treatment interrupted if neurotoxicity of grade 2 or more occurs at any point during therapy. Prior taxane use may not be a predictor of severe neurotoxicity, since a similar degree of neurotoxicity was observed by Robson et al. [19] who treated 17 patients with advanced breast cancer (11 taxane-naive and six taxane-resistant) with CT-2103 235 mg/m^2 every 3 weeks. In this study, four patients (24%) experienced grade 3 neuropathy that led to discontinuation of the

drug. The relationship to prior taxane exposure needs to be carefully evaluated in the future. Additional evidence to support independence of this toxicity from prior experience with taxanes is provided in the study by Norton et al. who treated 28 chemotherapy-naive patients who were ≥ 70 years of age or ECOG performance status 2 with CT-2103 at a dose of 175 mg/m^2 every 3 weeks [21]. Grade 3 or 4 neuropathy was seen in 5 (18%), a very substantial toxicity rate in this population. In our study, neurotoxicity was cumulative and prevented patients from receiving prolonged administration of CT-2103. It was not formally considered dose-limiting because it developed mainly after the second cycle, but we did not pursue further dose escalation because this level of toxicity was considered excessive. This unexpectedly high rate of cumulative neurotoxicity after only a small number of treatment cycles merits careful study in future trials of this agent.

Other studies have not shown the same degree of neurotoxicity, but all were early, or had few patients who received more than two cycles. In a phase I study of CT-2103 at doses of 235 and 270 mg/m^2 every 21 days in patients with advanced non-small-cell lung cancer, one of six patients had grade 2 neuropathy [18]. Phase I studies of CT-2103 in combination with carboplatin or cisplatin have also shown low rates of neurotoxicity [16, 17]. The maturation of these data is awaited with interest.

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