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Phase I clinical trial of the novel platin complex dicycloplatin: clinical and pharmacokinetic results

Su Li[1,2*], He Huang[1,3*], Hai Liao[1,2], Jing Zhan[1,2], Yin Guo[1,2], Ben-yan Zou[1,3], Wen-qi Jiang[1,3], Zhong-zhen Guan[1,3] and Xu-qing Yang[4]

[1]State Key Laboratory of Oncology in Southern China, [2]Department of Clinical Trial Center, Cancer Center, and [3]Department of Medical Oncology, Cancer Center, Sun Yat-Sen University, Guangzhou, Guangdong, and [4]Beijing Suo Pu Xing Da Pharmaceutical Co. Ltd. Beijing, China

Key words
dicycloplatin – Phase I clinical trial – toxicity – pharmacokinetics

Abstract. Translational relevance: Dicycloplatin (DCP) is a novel super molecule composed of carboplatin (CBP) and 1,1-cyclobutane dicarboxylate (CBDCA) joined by a strong hydrogen bond. The solubility and stability of platinum complexes have a direct bearing on their activity, toxicity and pharmacokinetics. Preclinical studies have shown that DCP overcomes the problem of CBP instability in aqueous solution and maintains anticancer effects. Clinical evaluation in a Phase I dose-escalation study in patients with tumors showed that DCP was tolerated at doses ranging from 100 to 550 mg/m^2 and had potential efficacy in Chinese cancer patients. DCP showed favourable bioavailability and stability in vivo, and the recommended Phase II dosage for DCP-containing chemotherapy is 450 mg/m^2. DCP is currently being investigated as a monotherapy in several cancer types, such as prostatic carcinoma, and in combination with paclitaxel in a Phase II non-lung cancer study. Purpose: Dicycloplatin (DCP) is a novel supramolecule composed of carboplatin (CBP) and 1,1-cyclobutane dicarboxylate (CBDCA) joined by a strong hydrogen bond. DCP is stable in aqueous solution unlike CBP alone. The purpose of this study was to assess the maximally tolerated dose, safety, and pharmacokinetics of DCP in Chinese cancer patients. Experimental Design: 29 patients were included in this study. DCP was administered by intravenous infusion over 1 hour once every 21 days. The dose of DCP was escalated from 50 mg/m^2 to 650 mg/m^2 using a modified Fibonacci scheme. Pharmacokinetic analysis was performed in 26 patients to determine the total and ultrafiltered platinum concentrations in plasma. Results: 29 and 20 patients were evaluated for toxicities and response, respectively. The primary adverse effects were nausea/vomiting (58.6%), thrombocytopenia (24.1%), neutropenia (17.2%), anemia (20.7%), fatigue (10.3%), anorexia (10.3%), liver enzyme elevation (10.3%) and alopecia (3.5%). There was no significant toxicity with doses up to 350 mg/m^2. At higher doses, a variety of dose-limiting toxicities (DLTs) were observed, including Grade 3/4 anemia, Grade 3/4 thrombocytopenia, and Grade 3/4 emesis under antiemetic treatment. The maximum tolerated dose of DCP was 550 mg/m^2. Two partial responses occurred in patients with non-cell lung cancer who had received cisplatin- or carboplatin-based chemotherapy. Plasma decay of total and free platinum concentrations was best fitted by using a two-compartment analysis. The terminal plasma half-life of total platinum after DCP administration ranged from 41.86 to 77.20 hours without significant dose dependency. However, the terminal plasma half-life of free platinum concentrations ranged from 42.34 to 61.07 hours. Conclusions: DCP displayed a favorable safety profile at doses between 50 mg/m^2 and 550 mg/m^2, and first efficacy signals were observed. DLTs were thrombocytopenia, anemia and emesis. The recommended starting dose for a subsequent Phase II study is 450 mg/m^2 once every 3 weeks.

*These authors contributed equally to this work.

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Correspondence to Dr. Zhong-zhen Guang Department of Medical Oncology, Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong, PR China guanzhzh@sysucc.org.cn

Introduction

Platinum compounds have become one of the most commonly used anticancer drugs for the treatment of a wide spectrum of human malignancies. Cisplatin was first synthesized in 1844 and became the first platinum-containing coordination complex. In the 1970s, the efficacy of cisplatin was established in human cancer patients with testicular, ovarian, bladder, lung and head

and neck malignancies [1, 2]. However, its clinical usefulness has frequently been limited by severe side effects such as nephrotoxicity, gastrointestinal toxicity, ototoxicity and neurotoxicity. Another concern is the emergence of tumor cells that are resistant to cisplatin after an initial response [3]. To overcome these unfavorable characteristics, ~ 3,000 platinum derivatives have since been synthesized and tested against cancer cells. Today, only four are currently used clinically: cisplatin, carboplatin, oxaliplatin, and nedaplatin [4]. Carboplatin has reduced renal and gastrointestinal toxicity compared with cisplatin. However, its dose-limiting toxicity is myelosuppression, chiefly thrombocytopenia [5].

Intramolecular hydrogen bonds make carboplatin self-associated in concentrated aqueous solutions where hydrogen bonds are formed between the ammonia molecules of one complex and the oxygen atoms of 1,1 – cyclobutane dicarboxylate (CBDCA) of neighbouring complexes. This association accounts for the long-term stability and ready-to-use infusion solutions of these ligands [6, 7]. However, when the formulation is diluted in either 5% dextrose or 0.9% NaCl in water, carboplatin is only stable for 8 hours at room temperature because its dicarboxylate chelate ligand is displaced in a stepwise manner by the attacking nucleophile [8]. To overcome the problem of carboplatin instability in aqueous solution, Yang et al. designed a novel super molecule, dicycolplatin (cis-diamine (1,1-cyclobutane dacarboxylate platinum (II): 1,1 cyclobutane dicarboxylic acid complex)) (DCP). DCP is composed of carboplatin and CBDC (at a 1 : 1 molecular ratio) joined through strong hydrogen bonds. Two types of hydrogen bonds were observed in the crystal structure: one type is between the hydroxyl groups of the CBDC and the carboxyl oxygen atoms of carboplatin, which forms two strong O-H···O hydrogen bonds, and the other is formed between the NH_3 groups of carboplatin and the oxygen atoms of CBDC [10]. DCP analysis by electrospray and mass spectrometry in negative ion mode showed one peak with an M/Z of 514.5, indicating that DCP exists as a complex of one molecule of carboplatin and one molecule of CBDC. This result was also verified in the plasma of patients who were administered DCP. DCP was still measureable at 2 hours after administration by monitoring the transitions (*m/z)* 514.5→143.1; the amount of carboplatin was lower than 30% of the original dose administration (Table 1).

Table 1. The DCP and CBP concentration in plasma determined by LC-MS/MS after intravenous infusion of 450 mg/m^2 of DCP over 1 hour.

Time (h)	DCP (μg/ml)	CBP (μg/ml)	Rate (CCBP/ CDCP)
0	0	0	
1.0	26.90	2.87	10.6
1.5	19.2	5.48	28.5
2.0	17.1	5.01	29.2

The self-associated or different intramolecular-associated complexes can circulate in blood during administration, which would have far-reaching implications for the transport, uptake and possibly the molecular mechanism of action. The structure of the super molecule DCP, formed by carboplatin and CBDC, is different from carboplatin, and thus its characteristics, such as stability, pharmacokinetics, and pharmacodynamics, also change [8].

Precipitation in the carboplatin solution was observed after ~ 1 week, and a black powder of platinum appeared; however, the solution of DCP remains clear for 10 years. DCP was shown to be more potent than carboplatin in vitro, requiring fewer DNA adducts to achieve equivalent cytotoxicity. In animal models, DCP has an enhanced therapeutic efficacy over carboplatin. DCP is more active against Lewis lung cancer human mammary tumor xenografts than carboplatin or a combination of carboplatin and CBDC, with ED50s of 4.87, 13.61, and 8.37 mg/kg, respectively [9]. A toxicity evaluation in beagles showed milder gastrointestinal effects, milder myelosuppression, and milder mucositis for DCP than carboplatin. It was expected that myelosuppression would be the DLT of DCP in clinical trials. These preclinical results are encouraging for the treatment of human solid malignancies. A Phase I clinical trial was performed to determine the maximum tolerated dose (MTD), evaluate the safety, and characterize the pharmacokinetics of a single dose treatment of DCP in patients with advanced solid cancers.

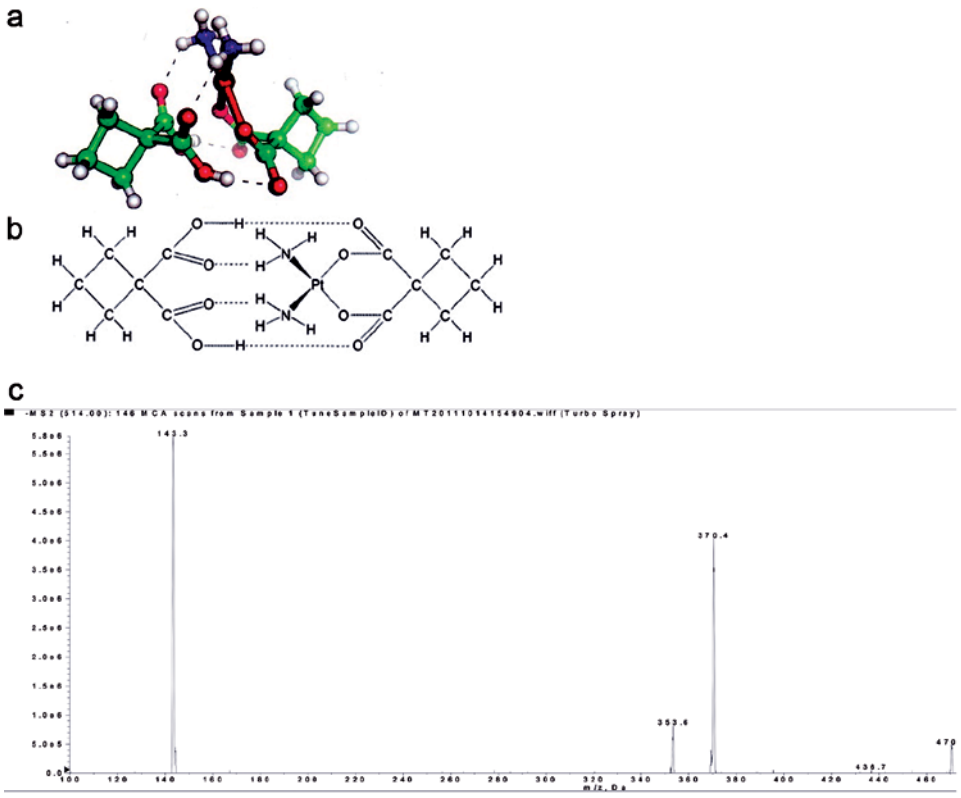

Figure 1. a: A computer generated structure model of the DCP supramolecular in the aqueous solution; b: the supramolecular structure of DCP in the aqueous solution; c: The mass spectrometry of DCP and its fragment ions *(m/z* 514/143).

Patients and methods

Eligibility

Patients who had tumors were nonresectable and/or had metastatic measurable tumors and had failed established treatment. Patients had no effective treatment options and were presented with an Eastern Cooperative Oncology Group performance status of 0 – 2 and a life expectancy of ≥ 3 months. Patient ages ranged from 18 to 65 years, and they gave signed, informed consent. Other eligibility requirements included adequate hematologic function (absolute neutrophil count ≥ 1,500/µl; platelet ≥ 100,000/µl; and haemoglobin ≥ 9.0 g/dl), renal function (a serum creatine level of 2 mg/dl or a creatine clearance ≥ 60 ml per min), and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels less than two times the upper normal limits. No prior chemotherapy, immunotherapy, or radiation therapy within 4 weeks was permitted. Patients with the following conditions were excluded: 1) a pre-existing peripheral neuropathy of Grade ≥ 2; 2) the presence of brain metastases, psychiatric disease, or seizure disorders; and 3) pregnant or lactating women. The studies were approved by the ethics committee of the Cancer Center, Sun Yat-sen University, China, and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study design and treatments

This was an open label, Phase I, accelerated dose-escalation trial investigating the tolerability and pharmacokinetics of a single DCP dose every 21 days in Chinese cancer patients. Every treatment cycle comprised a 21-day screening period, a 1-day treatment and a 3-week post visit. The recommended starting dose was 50 mg/m^2, which was equivalent to 10% of the lethal dose in mice (380 mg/kg).

No intra-patient dose escalation was allowed. The dose was escalated according to a modified Fibonacci scheme and followed a standard 3+3 design. A DLT was character-

ized by a World Health Organization (WHO) Grade 3 toxicity (except for alopecia and untreated nausea and emesis) and by all Grade 4 toxicities that occurred during the treatment.

Study assessments

Pre-treatment evaluation included a complete report of the patient's history, physical examination, and documentation of performance status. The pre-treatment laboratory evaluation included a complete blood count, a partial thromboplastin time, a urinalysis, blood chemistry (including liver function tests), and a viral hepatitis marker study. A creatinine clearance measurement at the 24-hour urine collection was performed. Complete blood, serum creatinine, and liver function tests were evaluated twice each week for the first 2 weeks and once for the third week. A patient's history, physical examination, and blood chemistry were performed every week during the study. Safety and tolerability of DCP were assessed by changes in incidence and severity of adverse events, a physical examination, vital signs (including 12-lead resting electrocardiogram), and laboratory examination according to the WHO. All forms of toxicity were managed properly if they occurred. Treatment was stopped if the disease progressed, Grade 4 toxicity occurred, the performance status of patients was ECOG (Eastern Cooperation Oncology Group) [4], or the patient refused further treatment.

Radiographic evaluation was performed at baseline and at the end of treatment to assess tumor response. The response criteria was defined as follows. 1) A complete response (CR) was defined as the absence of all evidence of tumors for at least 4 weeks and no evidence of a newly developed lesion. 2) A partial response (PR) was defined as a reduction of > 50% in the sum of the products of the longest perpendicular dimensions of indicator lesions for a period of at least 4 weeks and no evidence of an enlargement of the other lesions or any newly developed lesion. 3) Stable disease (SD) was defined as a reduction of < 50% or an increase of < 25% in measurable tumor area and no evidence of newly developed lesions for at least 4 weeks. 4) Progressive disease (PD) was defined as an increase of > 50% in the sum of the products of the longest perpendicular dimensions of indicator lesions or the presence of a newly developed lesion.

Pharmacokinetic sampling and analytical method

All patients underwent blood and urine sampling during DCP treatment. Blood samples (5 ml) were collected in heparinized tubes prior to infusion; at both 0.5 and 1 h during infusion; and at 0.25, 0.5, 1, 4, 8, 12, 24, 48, 72, 120, and 144 h after infusion. Plasma was separated by centrifugation, and an aliquot was passed through a Millipore Amicon Ultra centrifugal filter (0.5 ml, 30K membrane) to obtain ultrafiltered plasma. The protein-free ultrafiltrate and aliquots of whole plasma for platinum analysis were stored at –70 °C until further analyses. Complete urine specimens were collected for the measurement of renal clearance during the first day (0 – 4 h, 4 – 8 h, 8 – 12 h, 12 – 24 h) and every 24 hours for the next 2 days; the specimens were stored at –70 °C until they were analyzed.

The platinum concentrations in plasma (total platinum) and the ultrafiltered plasma (free platinum) were determined at 265.9 nm with a flameless atomic absorption spectrophotometer (Varian SpectrAA-40). The assays used for the quantification platinum were validated according to China State Food and Drug Administration guidelines. The assay was linear over the range from 0.05 to 5.00 μg/ml in all studies with an LLOQ of 0.05 μg/ml. The coefficient of variation (CV) for inter-run assays ranged from 3.8 to 6.3%, and for intra-run assays, the CV ranged from 7.6 to 10.3%. The pharmacokinetic parameters of platinum levels after DCP administration were estimated with the two-compartmental open model using WinNonlin (5.0). The following pharmacokinetic parameters for both total and free platinum were obtained by linear model fitting: the volume of distribution at a steady state (Vss); the distribution half-life ($t_{1/2\alpha}$); the terminal half-life ($t_{1/2\beta}$); total clearance (CL_T); and the area under the plasma concentration time curve (AUC) from time 0 to the last point (of collecting sample h) (AUC_{0-t}) or extrapolated to infinity ($AUC_{0-\infty}$). The renal clearance (CL_R) of

Table 2. The clinical characteristic of patients.

Characteristics		Number
Gender (male vs. female)		23 : 6
Age (year) (median age)		30 – 70 (50)
Performance status:	0	5 (17.24%)
	1	23 (79.31%)
	2	1 (3.45%)
Tumor type		
Nasopharyngeal carcinoma		10 (34.48%)
Colorectal		8 (27.59%)
Nonsmall-cell lung cancer		7 (24.14%)
Synoviosarcoma		1 (3.45%)
Malignant schwannoma		1 (3.45%)
Breast cancer		1 (3.45%)
Hodgkin's lymphoma		1 (3.45%)
Prior therapy		
Surgery		14 (48.28%)
Radiotherapy		16 (55.17%)
Prior chemotherapy		
Regimens		1 – 8 (average: 3.4)
Cycles		2 – 26 (average: 9.4)
Drugs		2 – 13 (average: 5.3)
Prior platinum		27 (93.10%)

Table 3. Number of patients with DLT in the once administration of DCP.

Dose level (mg/m^2)	No. of patients (n = 29)	Number escalated from previous dose (%)	Number with DLTs
50	3		
100	3	100	
175	3	75	
250	3	66	
350	3	50	
450	3	33.3	
550	8	16.7	1 Grade 4 thrombocytopenia
650	3	16.7	1 Grade 3 thrombocytopenia; 2 Grade 3/4 emesis

platinum after DCP administration was calculated as $\delta A_{0-t}/AUC_{0-t}$, where δA_{0-t} indicates the renal-excreted amount of platinum for 4 days after drug administration.

Results

Patient characteristics

In total, 29 patients were enrolled in the study between February 2004 and October 2005, and all were eligible for analyses. The patients' characteristics are listed in Table 2. The median age of patients was 50 years (range 30 – 70 years). 23 patients were male and 6 were female. There were 10 patients with nasopharyngeal carcinoma, 8 patients with colorectal tumors, 7 patients with lung tumors, and 4 patients with other tumors. All patients had received at least two prior chemotherapies, 20 patients had received prior cisplatin treatment, and 7 patients had received prior carboplatin treatment.

Safety and DLT

29 patients were all assessed for DCP safety. All patients experienced one or more adverse events, with at least 85% of patients experiencing one treatment-related adverse effect. Most treatment-related events were mild to moderate (WHO Grade ≤ 2) in severity at doses up to 350 mg/m^2. A variety of DLTs were observed at higher dosages: at 450 mg/m^2, 1 patient experienced Grade 4 anemia; at 550 mg/m^2, 1 patient experienced Grade 4 thrombocytopenia; and at 650 mg/m^2, 1 patient developed Grade 3 thrombocytopenia, 1 patient developed Grade 3 anemia, and 2 patients developed Grade 3/4 emesis under antiemetic treatment. Myelosuppressive effects were reversible and did not need supportive treatment; emesis was serious and required medical attention (for example, fluid replacement). As shown in Table 3, the MTD was 550 mg/m^2.

The major toxicities for all adverse effects are shown in Table 4, including thrombocytopenia (24.14%), neutropenia (17.24%), anemia (20.69%), nausea/vomiting (58.62%), fatigue (10.34%), anorexia (10.34%), alopecia (3.45%), and liver enzyme elevation (10.3%). Other toxicities that may or may not have been related to DCP treatment included serum creatine elevation (13.8%), alopecia (3.4%), dizziness (6.8%), blood-fasting sugar elevation (3.4%), hyponatremia (3.4%), and hypopotassemia (3.4%).

Myelosuppression, consisting of thrombocytopenia and neutropenia, was clearly dose related and dose limiting. Neutropenia was found in 5 patients, thrombocytopenia in 7, and both in 3 patients. Thrombocytopenia was observed at all doses above 350 mg/m^2. It was generally delayed, occurring 2 – 3 weeks after dosing, and often prolonged for 2 – 3 weeks; patients recovered from it without a platelet transfusion. Thrombocytopenia was mild and moderate at 350 and 450 mg/m^2, but became abruptly more pronounced at

Table 4. Treatment-related adverse events occurring in > 10% of treated patients.

Event	Grade	Dose Level (mg/m^2)								total			
		50	100	175	250	350	450	550	650	Grade (1 – 2)		Grade (3 – 4)	
		(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 8)	(n = 3)	No	%	No	%
Thrombocytopenia	1 – 2					1	1	1	2	5	17.2		
	3 – 4							1	1			2	6.8
Anemia	1 – 2				1		1	2		4	13.7		
	3 – 4						1		1			2	6.8
Nausea/vomiting	1 – 2			1	1	2	3	3	1	11	37.9		
	3 – 4		1					3	2			6	20.7
Leukopenia	1 – 2	1				1	1	1	1	5	17.2		
Neutropenia	1 – 2	1					1	2	1	5	17.2		
Creatinine elevation	1 – 2		2		1			1		4	13.7		
Total bilirubin elevation	1 – 2			2			1			3	10.3		
Anorexia	1 – 2							2	1	3	10.3		
Fatigue	1 – 2							3		3	10.3		

Table 5. Pharmacokinetic parameters of total platinum after intravenous infusion of 100 – 650 mg/m^2 of DCP over 1 hour.

PK Parameters	Dose level (mg/m^2)						
	100	175	250	350	450	550	650
	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 8)	(n = 3)
C_{max} (µg/ml)	2.23 ± 0.11	3.93 ± 0.07	6.62 ± 0.14	7.33 ± 0.91	13.43 ± 0.57	16.01 ± 6.23	17.10 ± 1.53
$t_{1/2\alpha}$ (hour)	1.32 ± 0.29	1.15 ± 0.86	1.49 ± 0.18	1.60 ± 0.55	1.18 ± 0.56	2.20 ± 1.05	17.10 ± 1.53
$t_{1/\beta}$ (hour)	57.29 ± 19.70	143.65 ± 85.08	100.75 ± 11.29	97.16 ± 52.14	99.39 ± 22.73	107.95 ± 23.25	88.17 ± 16.30
$AUC_{(0-t)}$ (µg/ml×h)	13.31 ± 0.93	39.52 ± 13.53	66.68 ± 7.78	106.60 ± 44.16	135.31 ± 34.45	151.17 ± 23.61	156.69 ± 15.21
$AUC_{(0-\infty)}$ (µg/ml×h)	17.56 ± 1.78	50.68 ± 22.05	108.32 ± 23.45	150.01 ± 104.61	164.02 ± 41.34	189.94 ± 90.33	205.85 ± 28.32
CL_T (l/h×m^2)	2.00 ± 0.39	1.07 ± 0.33	1.62 ± 0.16	1.10 ± 0.72	0.98 ± 0.18	0.89 ± 0.27	0.79 ± 0.06
V_{ss} (l/m^2)	157.24 ± 26.25	200.60 ± 61.79	233.87 ± 10.2.3	119.44 ± 32.97	137.68 ± 41.31	132.43 ± 28.27	183.91 ± 98.64
A_{0-t} (% of dos)	85.9 ± 8.3	78.6 ± 2.8	68.5 ± 5.4	87.6 ± 6.8	91.2 ± 3.4	87.8 ± 6.7	89.5 ± 4.3

V_{ss} = volume of distribution; Cl_T = total body clearance; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; AUC = area under the plasma concentration time curve; A_{0-t} = cumulative urinary excretion over the first 96 hours. Each entry represents the mean ± standard error of the 3 patients or 8 patients.

a higher dose level. At a dose of 550 mg/m^2, 1 of 6 patients experienced Grade 4 thrombocytopenia with a platelet count below 50,000/µl, and 1 patient experienced Grade 2 thrombocytopenia. At 650 mg/m^2, all 3 patients developed thrombocytopenia; 1 with Grade 3, 1 with Grade 2, and 1 with Grade 1.

Leukopenia occurred in 4 patients (1 patient with Grade 1 and 3 patients with Grade 2), and nadir was reached between Days 7 and 14. Neutropenia was mild to moderate. Only 1 patient who was administered DCP at 650 mg/m^2 had a neutrophilic granulocyte nadir of 1.2 × 109/l, and the patient recovered within 6 days. Although anemia was observed in 6 patients (2 patients with Grade 1; 2 patients with Grade 2; 1 patient with Grade 3; and 1 patient with Grade 4), it appeared to be related to the underlying disease rather than any drug-related phenomenon.

Nausea and vomiting were the most common nonhematologic toxic effects (58.62%). This gastrointestinal intolerance was experienced by nearly all patients, but it was generally mild and brief and did not require antiemetics at lower doses. Severe emesis, however, was experienced by 5 patients: 3 patients had relief with conventional doses of metoclopramide, but 2 patients had little or no relief with antiemetics, which did interfere with oral intake. Liver enzyme elevation was noted in 4 patients: 1 patient experienced a Grade 2 elevation in ALT levels; 2 patients experienced a Grade 1 elevation and 1 patient experienced Grade 2 AST levels. In all patients, AST values peaked on Day 7 and re-

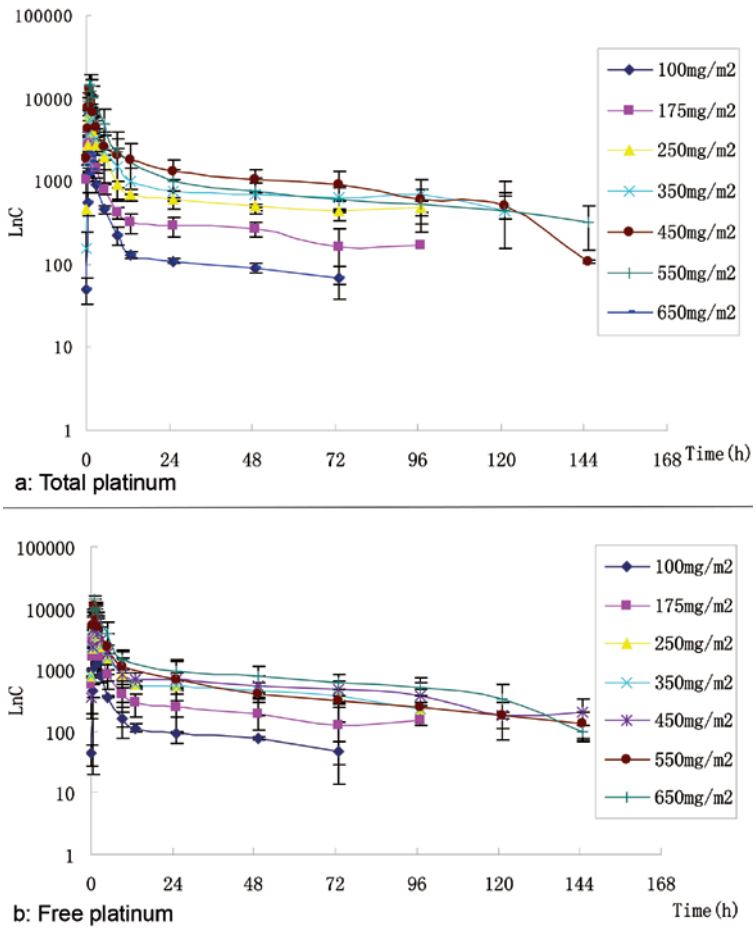

Figure 2. Plasma concentration time curves of platinum after patients received a single intravenous DCP infusion of 100 – 800 mg/m^2. Each point represents the mean of 3 or 8 patients. a: total platinum concentration. b: free platinum concentration.

turned to the baseline values within 3 weeks. Two patients showed a mild elevation of serum bilirubin levels at Day 7 after the dose, but the levels normalized within a week.

Serum creatine elevation was mild (Grade 1) and noted in 4 patients (24%). All other patients had stable serum creatinine levels throughout the observation periods, including 3 patients who had elevated levels resulting from prior cisplatin therapy. Three patients complained of fatigue, which was related to anemia. Alopecia (Grade 3) occurred in 1 patient who was treated with the highest dose. Pruritus, pain at the injection site, stomatitis and headache were rare and negligible. Grade 1 – 2 dizziness occurred in 2 cases.

There were no reports of tinnitus and no cases of clinically detectable motor neurotoxicity, skin toxicity, or sensory neurotoxicity. There were no reports of oral mucositis or anaphylactic-like reactions.

Anti-tumor response

Of the 29 patients enrolled in this study, only 20 had measurable disease and were evaluable for response. Two (10%) confirmed partial responses were observed in patients suffering from lung cancer after being treated with one cycle of DCP (550 mg/m^2). 13 patients (65%) remained stable, whereas 5 patients (25%) showed disease progression.

Pharmacokinetics

Pharmacokinetic data was available for 26 of the 29 patients. Pharmacokinetic data for 3 patients who were administered 50 mg/m^2 DCP was not included. A summary of the total and free platinum pharmacokinetic variables at each DCP dose level are presented in Figure 2a and 2b. Following infusion of a single dose of DCP at 100 mg/m^2 (n = 3), 175 mg/m^2 (n = 3), 250 mg/m^2 (n = 3), 350 mg/m^2 (n = 3), 450 mg/m^2 (n = 3), 550 mg/m^2 (n = 8), or 650 mg/m^2 (n = 3), platinum plasma concentrations reached a maximum at ~ 1 hour, declined quickly at 5 hours, and then slowly declined. Changes in plasma platinum concentrations after drug administration were best explained by a two-compartmental open model according to the Akaike criteria.

The mean maximum observed total platinum concentration (C_{max}) and the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) generally increased in a dose-proportional manner up to 650 mg/m^2 (Table 5). The mean terminal half-life ($t_{1/2}$) ranged from 41 to 77 hours across the 100 – 650 mg/m^2 doses and did not show any significant dose-dependent changes. Mean estimates of the volume of distribution based on body surface (Vss) ranged from 67 to 133 l/m^2 across the dose range (100, 175, 250, 350, 450, 550 and 650 mg/m^2 DCP) and were consistent with a large distribution of platinum into extravascular space.

However, time decay of the free plasma platinum concentrations after DCP administration showed a similar pattern compared with those of the total platinum concentra-

Table 6. Pharmacokinetic parameters of free platinum after intravenous infusion of 100 – 650 mg/m^2 of DCP over 1 hour.

PK Parameters	Dose level (mg/m^2)						
	100	175	250	350	450	550	650
	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 8)	(n = 3)
C_{max} (μg/ml)	2.03 ± 0.18	4.03 ± 0.44	6.20 ± 1.73	7.08 ± 0.51	8.27 ± 0.24	12.91 ± 3.07	14.23 ± 1.67
$t_{1/2\alpha}$ (hour)	1.38 ± 0.21	1.47 ± 0.40	2.11 ± 0.78	2.21 ± 0.67	1.78 ± 0.88	1.80 ± 0.59	1.79 ± 0.15
$t_{1/\beta}$ (hour)	99.67 ± 49.77	39.70 ± 12.39	94.83 ± 26.98	82.51 ± 14.89	134.60 ± 37.87	108.37 ± 98.60	65.39 ± 11.43
$AUC_{(0-t)}$ (μg/ml×h)	11.33 ± 1.09	21.80 ± 3.33	51.87 ± 17.57	68.09 ± 11.67	69.36 ± 34.20	94.21 ± 31.32	130.74 ± 38.70
$AUC_{(0-\infty)}$ (μg/ml×h)	18.41 ± 1.96	27.96 ± 9.53	78.50 ± 23.99	100.45 ± 48.99	136.10 ± 66.80	156.73 ± 47.58	187.56 ± 41.38
CL_T (l/h×m^2)	2.14 ± 0.29	2.52 ± 0.86	1.17 ± 0.72	1.22 ± 0.66	1.82 ± 0.98	1.97 ± 0.50	1.75 ± 0.74
V_{ss} (l/m^2)	301.74 ± 150.87	136.46 ± 4.16	142.30 ± 43.33	147.73 ± 93.03	334.09 ± 130.14	293.96 ± 234.68	157.09 ± 38.41

V_{ss} = volume of distribution; Cl_T = total body clearance; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; AUC = area under the plasma concentration time curve. Each entry represents the mean ± standard error of the 3 patients or 8 patients.

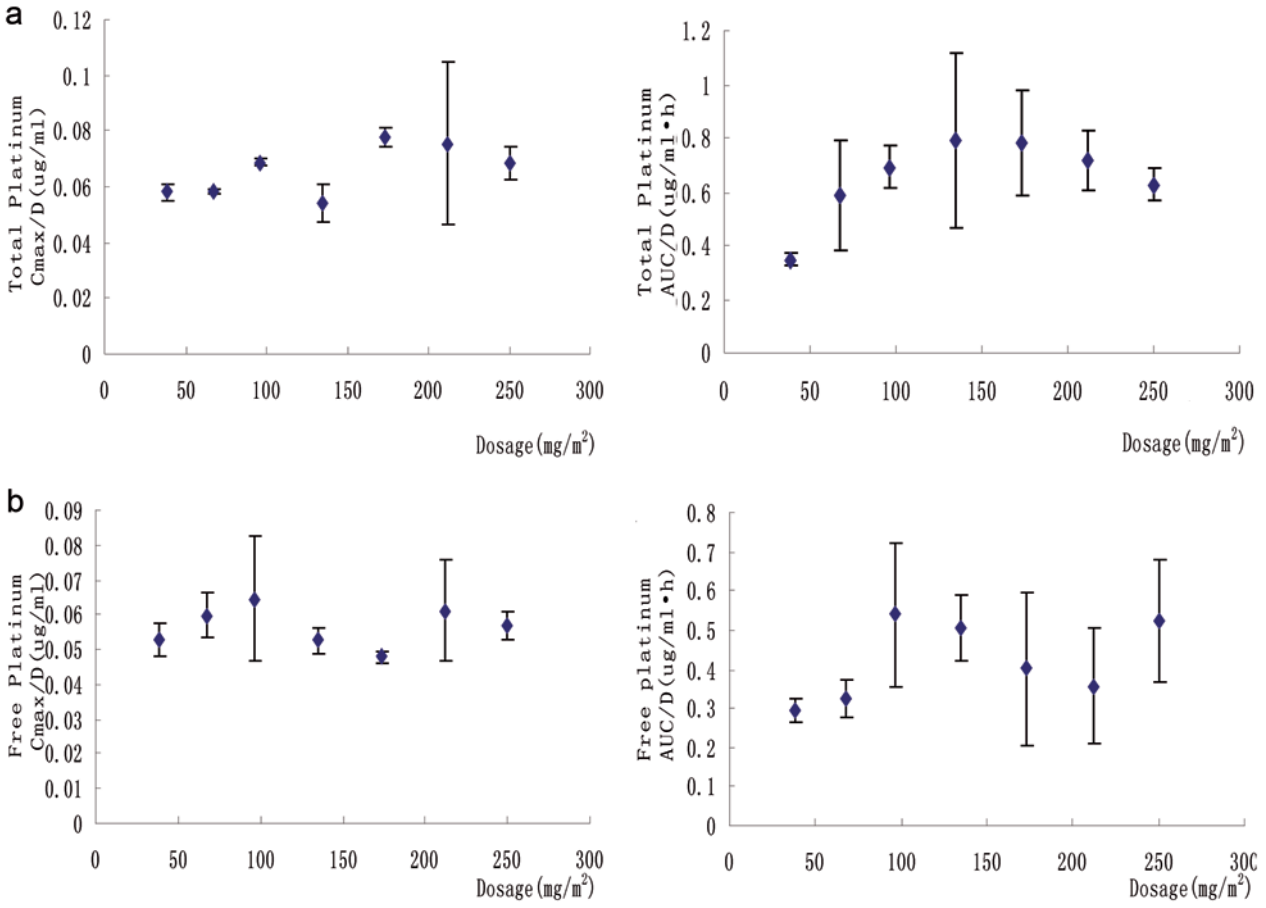

Figure 3. Platinum area under the concentration-time curve (AUC) versus Dicycloplatin (DCP) dose level and C_{max}/D versus Dicycloplatin (DCP) dose level (a): total platinum; (b): free platinum.

tion. The free drug ratio of the plasma platinum concentration after DCP administration was time-dependent, resulting in an initially high free drug ratio that implied the slow equilibration of protein binding in vivo (Figure 3). The mean maximum observed free platinum C_{max} and AUC increased in a dose-proportional manner up to 650 mg/m^2; their correlation coefficients were 0.9664 and 0.9648, respectively. At the end of the infusion, an average of 40 – 100% of the peak total plasma platinum was found to be ultrafiltered. The AUC of free platinum was smaller than that of the total platinum, but exhibited a dose-dependent, incremental pattern (Table 6). The V_{ss} of free platinum were greater than

40 l/m^2 and varied from 65 l/m^2 to 239 l/m^2 without showing any dose dependence. The CL of free platinum concentrations showed lower values with lower doses (100, 175 mg/m^2) compared with the high-dose groups. However, the CL_T of free concentrations showed constant values in the whole dose range used. The dose-normalized individual and mean C_{max} and AUC of free and total platinum as a function of platinum dose are shown in Figure 3. The dose-normalized free and total platinum exposure and C_{max} level did not increase or decrease across the dosage range of 100 – 650 mg/m^2. The cumulative urinary excretion for platinum over 48 hours ranged from 66 to 95% over the dosage range studied. In the first 4 hours after infusion, an average of 90% of the total DCP dose was recovered in the urine, as measured by total urinary platinum.

Discussion

The chemical structures of clinically used platinum anticancer drugs are quite diverse. Cisplatin, carboplatin and nedaplatin have two amine groups in the cis-orientation with two "leaving" groups – chloride, cyclobutane, or a glycolate moiety. These three platinum compounds yield the same active metabolite: diaqur-diamine-platinum, which reacts with amine groups of proteins, RNA, and DNA. This material yields platinum-DNA adducts, which appear to be associated with clinical anticancer activity. There could also be intermediate derivatives such as monochloro- or dichloro-diamine- platinum, i.e., carboplatin and nedaplatin could be assimilated to the precursors of cisplatin [4]. Hydrolysis is a key step for these three platinum compounds, and each of them has different kinetics. Cisplatin hydrolyses extremely rapidly, whereas carboplatin hydrolyses more slowly because methylene hydrogen atoms impede water molecules from attacking the platinum ion via the + and –z axis of the complex, thus reducing hydrolysis rates for carboplatin [7]. The rate of hydrolysis largely determines the chemical reactivity and intrinsic cytotoxicity of the complex, and the nature of the carrier ligand may influence the tissue distribution characteristics of the molecule. These 2 combined factors determine the unique chemical reactivity and disposition properties of a given platinum complex. DCP was introduced into clinical trials because in animal studies the agent was more stable while retaining antitumor activity [11].

The current study shows that the newly developed platinum complex, DCP, can be administered safely at doses up to 550 mg/m^2. At 650 mg/m^2, a variety of DLTs were observed, including myelosuppression and gastrointestinal toxicities. The DCP toxicity profile included myelosuppression and emesis, similar to carboplatin. However, DCP was associated with less severe myelosuppression than carboplatin. Anemia occurred in 6 patients (20%), but either the drug or the underlying disease may have contributed to this. Thrombocytopenia was severe in some patients at higher dose levels, and the decreased PLT percentage has a positive relationship with the AUC ($r = 0.772$). Leukopenia was generally moderate. No bleeding or hemolysis was observed in patients who had decreased hemoglobin. For patients with poor PS, the presence of bone metastasis or prior exposure to multiple myelosuppressive agents appeared to contribute more to myelosuppression.

Gastrointestinal toxicity was marked by moderate to severe nausea and vomiting that occurred even at the lower doses and was not clearly dose-related. DCP-induced emesis was much less intense and shorter in duration compared to cisplatin-induced emesis, but it was much more intense than carboplatin-induced emesis [12, 13]. The vomiting occurred in a few episodes per day and was long-lived. Vomiting typically could not be controlled by regular antiemetics, and this influenced oral intake at the highest dose. Patients who could not tolerate cisplatin-induced nausea also did not accept DCP.

It has been reported that the total clearance of ultrafiltrable platinum correlated with creatine clearance, that patients with poor renal function had a higher AUC for platinum and that there was a positive correlation with the degree of thrombocytopenia. We observed that patients with mildly impaired creatine clearance did not develop increased hematologic toxicity. Because all but 3 patients had a mildly abnormal elevation in serum creatinine, there was no increased risk. We did not study patients with high degrees of renal dysfunction.

Pharmacokinetic studies showed the pattern of biphasic decay of total and free platinum. The AUC and C_{max} of total platinum tended to increase proportionally with dose. The ratio of free platinum over total platinum concentration appeared to be time- and concentration-dependent, but the dependence was nonlinear. This nonlinear relationship in protein binding caused a difference in the pharmacokinetic profile between the total and free platinum of DCP and produced dose-dependent changes in free platinum kinetics. At low doses (ranging from 100 to 350 mg/m^2), the plasma protein binding was ~ 10% at 1 hour after administration, but at the higher doses (ranging from 450 to 650 mg/m^2), it was ~ 40 – 80%, compared to 18% for carboplatin and 60 – 80% for cisplatin [14, 15]. The terminal half-life of free platinum was similar to that of total platinum (89.30 hours compared to 99.14 hours across all doses) and was much longer than those of carboplatin (2.2 h) or cisplatin (0.3 – 05 h). The volume of distribution of free platinum was slightly larger than that of total platinum and much larger than those of carboplatin (17.0 l) or cisplatin (19.2 l). This data indicates that DCP is much more bioavailable. The elimination of platinum occurred mainly in urine rather than in faeces. Over a 2-day period, the majority of the platinum (65.8 – 94.6%) was excreted in urine. All pharmacokinetic parameters displayed moderate to high variability after a single dose.

Two patients with lung cancer showed partial anti-tumor activity in this study. These 2 patients had tumor progression after cisplatin or carboplatin-containing chemotherapy but experienced clinical benefits with DCP administration, suggesting the possibility that patients can overcome cisplatin or carboplatin-resistance. In addition, these 2 patients received 550 mg/m^2 of DCP, a dose equal to 360 mg/m^2 of carboplatin.

In summary, DCP was tolerated at doses ranging from 100 mg/m^2 to 550 mg/m^2, and the recommended Phase II dosage for DCP-containing chemotherapy is 450 mg/m^2. The primary DLTs were myelosuppression and emesis. DCP showed favourable bioavailability and stability in vivo; therefore, further clinical trials are warranted.

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