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ZD0473 pharmacokinetics in Japanese patients: a Phase I dose-escalation study

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Abstract

ZD0473 is new platinum agent that was rationally designed to circumvent platinum resistance and reduce the potential for nephro- and neurotoxicity. This Phase I dose-escalating study investigated the pharmacokinetics, tolerability and efficacy of ZD0473 in Japanese patients with solid, refractory tumours. ZD0473 was administered as a 1-h intravenous infusion every 3 weeks. Nine patients received a total of 16 cycles of ZD0473 (median 1 cycle/patient), with 3 patients treated at each of 3 doses (60, 90, 120 mg/m^2). The maximum plasma concentration (C_{max}) and the area under the concentration–time curve to infinity ($AUC_{0-\infty}$) increased with dose in a linear fashion for both total platinum and ZD0473 in plasma ultrafiltrate, suggesting that the pharmacokinetics of ZD0473 are linear. Haematological and non-haematological toxicities such as nausea and vomiting were mild (grade 1 or 2) and transient. No clinically significant nephro-, oto- or neurotoxicity was observed. Dose-limiting toxicity (DLT) was not observed and the maximum tolerated dose (MTD) was not identified. ZD0473 treatment showed evidence of disease stabilisation in 3 patients (33%). In conclusion, ZD0473 appears to have linear pharmacokinetics, and an acceptable tolerability profile at doses up to 120 mg/m^2 in Japanese patients with refractory solid malignancies. Following evaluation of the data from all the Western trials, the ZD0473 development programme changed and this Japanese trial was stopped.

Keywords: Chemotherapy; Refractory solid tumours; Pharmacokinetics; ZD0473

1. Introduction

Antitumour platinum complexes have been widely used for the treatment of various solid tumours such as ovarian, testicular, head and neck, bladder, small-cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC). Cisplatin is a first-generation platinum agent associated with excellent antitumour effects; however, this agent can cause serious adverse events such as gastrointestinal toxicity, nephro-, oto- and neurotoxicity [1]. Because of the toxicity associated with first-generation platinum agents, second-generation agents such as carboplatin and nedaplatin were developed. Carboplatin is associated with less nephrotoxicity and gastrointestinal toxicity than cisplatin, with myelosuppression (particularly thrombocytopenia) being the predominant adverse event [1]. In addition, among solid tumours, there is a considerable level of resistance to these platinum agents. Therefore, the development of newer platinum agents, which cause less adverse events and can circumvent platinum resistance, has been awaited with interest.

ZD0473 was rationally designed to overcome the major mechanisms of platinum resistance and reduce the potential for nephro- and neurotoxicity [2]. The initial Phase I dose-escalation study evaluated ZD0473 at doses from 12–150 mg/m^2 [3]. The dose-limiting toxicity (DLT) associated with ZD0473 treatment was myelosuppression (reversible thrombocytopenia) and was dependent on prior treatment [3]. The maximum tolerated dose was

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130 mg/m^2 in patients pretreated with ≤7 chemotherapy regimens and 150 mg/m^2 in patients pretreated with ≤4 regimens. The recommended dose for Phase II studies was 120 mg/m^2, with the option to escalate to 150 mg/m^2 if the dose was well tolerated [3]. ZD0473 has shown antitumour activity in Phase I and II trials in a wide range of solid tumours including ovarian, SCLC, hormone-refractory prostate cancer, and metastatic breast cancer [4–6].

Phase I studies in Western cancer patients have suggested that ZD0473 has linear pharmacokinetics in terms of both total platinum and ZD0473 concentrations in plasma, and that the area under the concentration-time curve (AUC_{0-t}) and the maximum plasma concentration (C_{max}) increase with dose [3,7,8]. In addition, plasma AUC_{0-t} correlated with thrombocytopenia and elimination of ZD0473 was shown to be triphasic [9]. The present article summarises the main findings from a Phase I study that investigated the pharmacokinetics and tolerability profile of ZD0473 in Japanese patients with solid, refractory tumours. A secondary objective of this trial was assessment of the efficacy of ZD0473 in these patients.

2. Patients and methods

2.1. Patients

Japanese patients with histologically or cytologically confirmed solid malignant tumours, which had not responded to standard therapy (or for which no appropriate therapy was available) were entered into this Phase I, dose-escalating study. Other eligibility criteria included: creatinine clearance ≥60 mL/min; age ≥20 and <75 years; World Health Organization (WHO) performance status ≤1; and an anticipated life expectancy of ≥12 weeks. Patients were also required to have adequate haematological, renal and hepatic function. Patients who had received systemic anticancer therapy or therapy with investigational agents within 4 weeks of the trial, and those who had received ≥4 previous chemotherapy regimens or extensive radiotherapy, were not permitted. The study was approved by the local ethics committee and written, informed consent was obtained from each patient.

2.2. Treatment

Five different ZD0473 dose levels were planned (60, 90, 120, 150, and 180 mg/m^2). ZD0473 was administered by a 1-h intravenous infusion on day 1 of each cycle. Before each subsequent cycle of treatment, all patients had to meet the following retreatment criteria: neutrophils ≥1500/mm^3; platelets ≥10×10^4/mm^3; serum creatinine <1.25 × upper limit of reference range (ULRR); total bilirubin <1.5 × ULRR; and non-haematological toxicity recovered to ≤grade 2 (diarrhoea to ≤grade 1).

Three patients were included at each dose level, and 3 additional patients were recruited to the same dose level if DLT was observed in 1 out of the 3 patients. DLT was defined as absolute neutrophil count <500/mm^3 associated with ≥grade 2 fever or infection or lasting >5 days; platelet count <25000/mm^3 or necessity of platelet transfusion; grade 3 parenchymatous toxicity or grade 4 non-haematological toxicity (except for nausea/vomiting in patients not receiving optimal antiemetics); or unresolved toxicity causing the next cycle of treatment to be delayed beyond day 43. Dose-escalation was dependent on the number of patients experiencing DLT; if no DLT was observed, patients were recruited to the next dose level.

2.3. Tolerability and efficacy assessments

Pretreatment evaluation included a medical history, medical examination, haematological and biochemical (including creatinine clearance) analyses, and an electrocardiogram. Assessments of tumour and serum tumour markers were also performed. Similar evaluations were carried out during treatment, but also included recording of adverse events (National Cancer Institute Common Toxicity Criteria) and tumour response (WHO response criteria). Adverse events were continuously recorded throughout the study, whereas tumour response was recorded before and after each cycle of treatment (on days 1 and 22) and at treatment completion/withdrawal.

2.4. Pharmacokinetic assessments

Blood and urine samples for pharmacokinetic analysis were collected during cycle 1 of therapy. Blood samples were collected pre-dose, during infusion (at 0.5 h) and at the end of infusion (at 1 h) and then at the following times after the end of each infusion 0.25, 0.5, 1, 3, 5, 9, 23, 47, 71, 167, 335, and 503 h. During additional cycles, a sample was obtained just prior to the start of ZD0473 administration. Urine samples were collected (first cycle only) pre-dose, and 0–12, 12–24, 24–48, and 48–72 h after completion of the ZD0473 infusion.

Plasma, plasma ultrafiltrate and urine samples were assayed for total platinum using a validated atomic absorption spectrophotometric assay [10]. Plasma ultrafiltrate and urine samples were also assayed for ZD0473 using a stable-isotope liquid chromatography/electrospray ionisation/tandem mass spectroscopy (LC/MS/MS) dilution assay [8,11]. The plasma ultrafiltrate concentration-time data for ZD0473 were evaluated using the compartmental analyses software, WinNonlin Professional version 3.1. The pharmacokinetic parameters derived were: C_{max}; time to C_{max} (T_{max}); terminal half-life ($t_{1/2}$); volume of distribution at steady state (V_{ss}); AUC_{0-t}; AUC to infinity ($AUC_{0-\infty}$); mean residence time (MRT); plasma clearance (CL); and total ZD0473 excreted into urine (Ae∞).

Table 1
Patient characteristics

No. patients	9
Males/females	3/6
Median age, years (range)	59 (43–69)
Performance status	
0	4
1	5
Site of primary tumour	
Colorectal	6
NSCLC	2
Sarcoma	1
Prior therapies	
Chemotherapy	3
Chemotherapy + surgery	6

3. Results

3.1. Patients

Nine patients (3 male, 6 female) with refractory solid tumours were entered into this study between June 2001 and November 2001. Patient baseline characteristics are shown in Table 1. All had a good WHO performance status and their median age was 59 years (range 43–69 years). The site of the primary tumour was colorectal in 6 patients, 2 patients had NSCLC and the remaining patient had sarcoma.

3.2. Treatment

All patients were pretreated with chemotherapy (<4 cycles/patient). The patients received a total of 16 cycles of ZD0473 (median 1 cycle/patient, range 1–5 cycles), with 3 patients treated at each of 3 doses (60, 90, 120 mg/m^2).

3.3. Tolerability

ZD0473 treatment had an acceptable tolerability profile up to doses of 120 mg/m^2 and was associated with no unexpected toxicities. The treatment-related adverse events that occurred in cycle 1 are presented in Table 2. Haematological toxicities included grade 1 or 2 leucopenia, neutropenia and anaemia. Non-haematological toxicities, such as nausea and vomiting, were generally mild and easily controlled. None of the patients experienced grade 3 or 4 toxicities. ZD0473 treatment was not associated with any clinically significant nephro-, oto- or neurotoxicity and DLT was not observed.

Table 2
Incidence of treatment-related adverse events (cycle 1)

	ZD0473 dose (mg/m^2)					
	60 ($n = 3$)		90 ($n = 3$)		120 ($n = 3$)	
	grade 1	grade 2	grade 1	grade 2	grade 1	grade 2
Haematological						
Leucopenia	0	0	0	0	1	0
Neutropenia	1	0	1	0	1	0
Lymphocytopenia	0	1	0	0	0	1
Anaemia	2	0	0	0	2	0
Non-haematological						
Nausea	0	1	1	0	1	0
Vomiting	0	1	0	1	1	0
Anorexia	0	1	1	0	0	0
Headache	1	0	0	0	1	0
Abdominal pain	0	0	0	0	1	0
Constipation	1	0	1	1	0	0
Diarrhoea	0	0	0	0	1	0
Alopecia	0	0	1	0	0	0
Albuminuria	1	0	0	0	0	0

3.4. Activity

Although response to therapy was not the primary endpoint of this study, all 9 patients were evaluated for response. ZD0473 treatment showed evidence of disease stabilisation in 3 patients (33%) treated at 60 mg/m^2 or 120 mg/m^2 ZD0473. The site of primary tumour in two of the three patients was NSCLC and one had colorectal cancer; these patients had stable disease for 5.9, 18.7, and 11.0 weeks, respectively. The patient who experienced the longest duration of stable disease was a 52-year-old male patient with NSCLC who had been pretreated with 4 cycles of a cisplatin and vinorelbine combination. This patient also experienced a 19% reduction in the size of the target lesion.

Table 3
Pharmacokinetic parameters for total platinum in plasma and plasma ultrafiltrate

	Plasma ZD0473 dose (mg/m^2)			Plasma ultrafiltrate ZD0473 dose (mg/m^2)		
	60 ($n = 3$)	90 ($n = 3$)	120 ($n = 3$)	60 ($n = 3$)	90 ($n = 3$)	120 ($n = 3$)
Mean C_{max}, μg/L (CV%)	2250 (5.04)	3460 (2.08)	4690 (9.98)	1810 (4.37)	3010 (8.04)	4440 (8.95)
Median T_{max}, h (range)	0.92 (0.92–1.00)	0.92 (0.92–1.00)	0.92 (0.92–1.00)	0.92 (0.92–1.25)	0.92 (0.92–1.00)	0.92 (0.92–1.00)
Mean $AUC_{0-\infty}$, μg.h/L (CV%)	155000 (33.8)	205000 (10.7)	281000 (12.3)	5920 (38.3)	7580 (15.5)	11800 (19.1)
Mean CL, L/h/m^2(CV%)	0.201 (33.8)	0.227 (10.7)	0.221 (12.3)	5.25 (38.3)	6.17 (15.5)	5.29 (19.1)
Mean V_{ss}, L/m^2 (CV%)	59.0 (15.9)	57.9 (19.5)	58.4 (8.17)	196 (50.6)	107 (4.72)	174 (46.0)
Mean MRT, h (CV%)	292 (21.2)	255 (19.9)	264 (4.47)	37.3 (102)	17.3 (15.9)	32.9 (68.1)
Median $t_{1/2}$, h (range)	229 (183–257)	169 (158–218)	205 (194–212)	45.8 (35.1–119)	32.0 (31.0–33.4)	77.2 (40.2–81.7)

Mean, geometric mean; CV, coefficient of variation.

Table 4
Pharmacokinetic parameters for ZD0473 in plasma ultrafiltrate

	ZD0473 dose (mg/m^2)		
	60 ($n = 3$)	90 ($n = 3$)	120 ($n = 3$)
Mean C_{max}, μg/L (CV%)	3750 (9.68)	6380 (12.2)	7530 (9.42)
Median T_{max}, h (range)	1.00 (1.00–1.25)	1.00 (1.00–1.00)	1.00 (1.00–100)
Mean $AUC_{0-\infty}$, μg.h/L (CV%)	5260 (13.2)	10800 (14.9)	12000 (4.53)
Mean CL, L/h/m^2 (CV%)	11.4 (13.2)	8.36 (14.9)	10.0 (4.53)
Mean V_{ss}, L/m^2 (CV%)	12.0 (6.73)	8.34 (19.3)	9.53 (7.97)
Mean MRT, h (CV%)	1.05 (11.8)	1.07 (6.27)	0.95 (4.70)
Median $t_{1/2}$, h (range)	0.91 (0.82–0.98)	0.83 (0.79–0.95)	0.83 (0.82–0.91)

Mean, geometric mean; CV, coefficient of variation; CL_R, renal clearance.

3.5. Pharmacokinetics

The mean pharmacokinetic parameters for total platinum in plasma and plasma ultrafiltrate are presented in Table 3. The C_{max} and the $AUC_{0-\infty}$ for total platinum in plasma and plasma ultrafiltrate increased with increasing dose, suggesting linear pharmacokinetics.

The mean pharmacokinetic parameters for ZD0473 in plasma ultrafiltrate are shown in Table 4. Both C_{max} and the $AUC_{0-\infty}$ for ZD0473 in plasma ultrafiltrate increased with dose in a linear fashion, with low variability (<13% for C_{max} and <15% for $AUC_{0-\infty}$). The data suggest that the pharmacokinetics of ZD0473 are linear and are consistent with previous observations for ZD0473 [7]). In general, C_{max} of ZD0473 in plasma ultrafiltrate were observed by the end of the 1-h infusion. The $t_{1/2}$ of ZD0473 in plasma ultrafiltrate was <1 h and this was consistent across the entire dose range. ZD0473 was almost undetectable in plasma ultrafiltrate by 10 h after dose administration (Fig. 1). Approximately 20% of the ZD0473 dose was excreted unchanged into the urine within 12 h of the infusion.

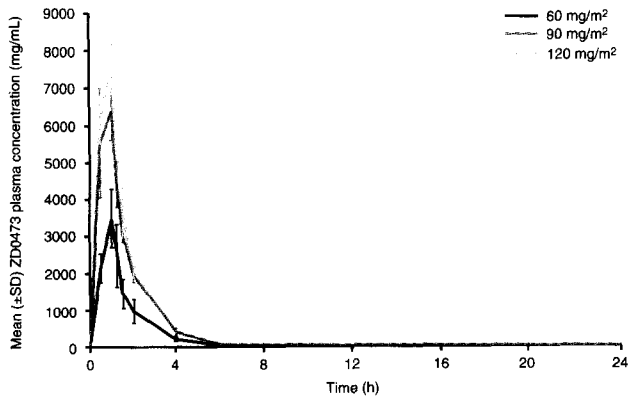

Fig. 1. Mean (±SD) ZD0473 concentration-time curves in plasma ultrafiltrate.

4. Discussion

In Japanese patients with a selection of refractory, solid malignancies, ZD0473 had an acceptable toxicity profile for all three doses (60, 90 and 120 mg/m^2) which was consistent with previous studies in Western patients [4,7,10]. ZD0473 showed evidence of antitumour activity, with three patients (33%) experiencing disease stabilisation.

The pharmacokinetics of ZD0473, in terms of $AUC_{0-\infty}$ and C_{max} increase with dose in a linear fashion in Japanese patients, which was in agreement with data obtained in Western studies using this agent [7]. Similarly, total platinum in plasma and plasma ultrafiltrate also increase with dose in a linear fashion. The pharmacokinetics of carboplatin are also linear [11,12], however, in contrast, exposure to free cisplatin is non-linear and depends on parameters such as infusion duration, dose, and urine flow rate [13]. $AUC_{0-\infty}$ and C_{max} also increase with dose with cisplatin and carboplatin [1,14], however, with carboplatin, this observation appears to be more clearly defined in patients with ovarian cancer than in those with other malignancies [12].

Evaluation of data from all Western ZD0473 trials showed that ZD0473 was an active drug in a range of tumour types and has a manageable toxicity profile. However, data from Phase II studies, particularly in ovarian and lung cancer indicated that ZD0473 was not able to overcome platinum resistance, therefore the focus of the ZD0473 development programme changed and this Japanese trial was stopped.

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