Cancer Chemother Pharmacol (2003) 52: 277–281
DOI 10.1007/s00280-003-0633-9

ORIGINAL ARTICLE

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A phase I study of ZD0473 combined with paclitaxel for the treatment of solid malignancies

Received: 27 September 2002 / Accepted: 25 March 2003 / Published online: 25 June 2003

Abstract *Purpose*: ZD0473 is a cytotoxic platinum agent, which in preclinical studies has exhibited synergistic activity when combined with paclitaxel. The aim of this open-label phase I study was to determine the maximum tolerated dose (MTD), safety, and antitumour activity of ZD0473 followed by paclitaxel in patients with refractory solid malignancies. *Methods*: Patients received paclitaxel and ZD0473 on day 1 every 3 weeks. Seven dose levels were planned (ZD0473 60–180 mg/m^2, paclitaxel 135–175 mg/m^2), with dose escalation dependent on the incidence of dose-limiting toxicity. *Results*: Included in the study were 23 patients who received 76 treatment cycles at dose levels 1 (60 mg/m^2 ZD0473, 135 mg/m^2 paclitaxel) to 6 (150 mg/m^2 ZD0473, 175 mg/m^2 paclitaxel). Dose-limiting thrombocytopenia (platelet count $<25\times10^9$/l) occurred in two of six patients at dose level 6, which defined the MTD. Grade 3/4 haematological toxicities included: anaemia (21.7%), neutropenia (39.1%), thrombocytopenia (34.8%), and leucopenia (34.8%). The most common grade 3/4 non-haematological toxicities included: alopecia (13.0%), pleural effusion (13.0%), somnolence (8.7%), and vomiting (8.7%). Of the 23 patients, 11 (47.8%) had disease stabilization, including 4 with non-small-cell lung cancer (NSCLC) who had a ≥25% reduction in tumour dimensions. *Conclusions*: ZD0473 combined with paclitaxel has a manageable tolerability profile and shows some evidence of antitumour activity in patients with NSCLC.

Keywords Paclitaxel · Refractory solid malignancies · ZD0473

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Introduction

Platinum agents are widely used as first-line therapy in the treatment of solid tumours. However, their efficacy is limited by both inherent and acquired resistance mechanisms [8] and the development of neurotoxicity in some patients [7]. Paclitaxel is one of the cytotoxics most widely combined with platinum agents to increase treatment efficacy. The main toxicity associated with paclitaxel treatment is myelosuppression, primarily neutropenia [2, 10]. Platinum-based combination chemotherapy regimens are the mainstay of current treatments for many advanced solid malignancies, including lung and ovarian cancers. Despite the superior response rates and prolonged survival times gained with platinum-taxane combinations, over 50% of patients with advanced ovarian cancer will eventually relapse and die from their disease [3]. Five-year survival rates for small-cell-lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) are also low at approximately 15% [14].

ZD0473 is a new platinum agent that was rationally designed to overcome platinum resistance. Preclinical in vitro studies showed synergistic activity with ZD0473 in combination with paclitaxel, gemcitabine, topotecan or vinorelbine [9]. In phase I/II studies, ZD0473 monotherapy had antitumour activity against a range of tumours including ovarian and lung cancer [5, 15]. In contrast to cisplatin, to date no clinically significant nephro-, neuro-, or ototoxicity has been observed with ZD0473. As with paclitaxel, myelosuppression is the

main dose-limiting toxicity (DLT) of ZD0473 [6]. The aim of this study was to evaluate the tolerability and efficacy of ZD0473 in combination with paclitaxel in patients with refractory solid malignancies.

Methods

Study design

This was a dose-escalating, phase I trial to determine the DLT, maximum tolerated dose (MTD) and recommended dose (RD) of ZD0473 when given in combination with paclitaxel to patients with refractory solid malignancies. Secondary objectives included evaluation of the safety and antitumour activity of this combination. This study was conducted in accordance with the principles of the Declaration of Helsinki, with the approval of institutional review boards or ethical committees and with the written informed consent of all patients prior to inclusion in the study.

Treatment

ZD0473 and paclitaxel were administered by intravenous infusion on day 1 of each 3-week cycle. Paclitaxel was administered over 3 h, followed 30 min later by ZD0473 over 1 h. ZD0473 was provided by AstraZeneca as an isotonic 0.4-mg/ml ready-to-use solution. It is light sensitive so was protected from the light during manipulation and administration. Seven dose levels were originally planned (ZD0473 60–180 mg/m^2, paclitaxel 135–175 mg/m^2), with at least three patients recruited at each dose level. Patients could receive up to six cycles of treatment. Intrapatient dose escalation was permitted if the patient had experienced only mild toxicity (not more than grade 1 treatment-related neutropenia or thrombocytopenia and/or not more than grade 1 treatment-related non-haematological toxicity) after receiving one or more cycles of treatment.

Blood samples were collected for analysis of ZD0473 (predose, end of infusion, then 2, 6 and 24 h, and 5, 8 and 15 days after treatment) and carboplatin (predose, end of infusion, then 2, 6, 24 and 48 h after treatment) pharmacokinetics.

Patients

Patients with refractory solid tumours for which no effective treatment exists were eligible. All were a minimum of 18 years of age, with a life expectancy of at least 12 weeks and a World Health Organization (WHO) performance status of 0 or 1. Other eligibility criteria included absolute neutrophil count (ANC) $\geq 1.5\times10^9$/l, platelets $\geq 100\times10^9$/l and haemoglobin ≥ 9 g/dl; creatinine clearance ≥ 60 ml/min (calculated using the Cockcroft-Gault formula); serum bilirubin not more than 1.25 times the upper limit of the reference range (ULRR); alanine and aspartate aminotransferases less than 2.5 times the ULRR in the absence of liver metastases and less than 5 times the ULRR if liver metastases were present. Patients were excluded if they had received more than one prior line of platinum-based therapy or more than six cycles of carboplatin as were those in whom more than 30% of the bone marrow had been irradiated.

Tolerability assessments

Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC). DLT was defined as any of the following experienced during the first cycle: ANC $< 0.5\times10^9$/l associated with fever or infection of grade 2 or more; ANC $< 0.5\times10^9$/l for at least 7 days; platelet count $< 25\times10^9$/l; grade 3/4 treatment-related non-haematological toxicity (except for alopecia, nausea or vomiting in patients not receiving optimal antiemetic medications); or treatment delay of more than 3 weeks due to unresolved toxicity. Full blood counts were measured weekly during treatment. Non-haematological toxicity was recorded throughout each cycle.

Dose escalation was based upon the number of patients experiencing DLT. Three patients were initially treated at each dose level with a further three added if a DLT was seen. If none of three or one of six patients had DLT, patients were escalated to the next dose. If two of six patients experienced DLT this was designated the MTD and the RD would be one dose level lower. However, if two or more of three or three or more of six patients had DLT, this was designated a toxic dose, with the MTD one dose level below and the RD two dose levels below.

Activity assessments

Antitumour activity was assessed by objective measurement of measurable lesions (diameter > 20 mm). Tumour response was assessed after every second cycle of treatment and at withdrawal using Response Evaluation Criteria in Solid Tumours (RECIST) criteria [16].

Results

Patient demographics

Included in the study were 23 patients, most of whom had a performance status of 1 at baseline (87.0%). The primary tumour in most patients (65.2%) was NSCLC and most had metastatic disease (73.9%). The majority of patients (87.0%) had previously been treated with a platinum agent (mean three cycles per patient); only one patient was chemonaive. Baseline patient demographics are presented in Table 1.

Treatment

A total of 76 cycles of treatment (mean three cycles per patient) were administered at dose levels 1 to 6 (Table 2). One patient at dose level 1, and two at dose level 6, had their doses reduced because of unresolved toxicity and no intrapatient dose escalation occurred.

Tolerability

All patients were evaluable for treatment tolerability. The most frequently encountered grade 3/4 haematological and non-haematological toxicities are shown in Table 3. The most common haematological adverse events (all grades) included anaemia (60.9%), neutropenia (60.9%), thrombocytopenia (56.5%), and leucopenia (56.5%). The most common non-haematological adverse events (all grades) included alopecia (65.2%), nausea (43.5%), asthenia (43.5%), and increased cough (43.5%). Most of these events were mild or moderate in severity (grade 1 or 2). No clinically significant neuro-, nephro- or ototoxicity was observed. Two patients at dose level 6 experienced DLT; both had thrombocytopenia, which led to treatment delay in one of them. Dose level 6

Table 1 Patient demographics

Total no. of patients	23
Male/female	15/8
Age (years)	
Median	58
Range	40–69
Primary tumour	
NSCLC	15
SCLC	2
Mesothelioma	4
Ovarian	1
Cervical	1
Metastatic site	
Lung	6
Liver	5
Bone	7
Lymph node	7
Pleural effusion	4
Other	7
None	6
WHO performance status	
0	3
1	20
Prior therapy[a]	
Chemo/immuno/hormonal therapy	22
Platinum therapy	20
Radiotherapy	11
Surgery	6
Other	3

[a]Prior therapies are not mutually exclusive

(150 mg/m^2 ZD0473, 175 mg/m^2 paclitaxel) was therefore the MTD; the RD for future studies would be dose level 5 (120 mg/m^2 ZD0473, 175 mg/m^2 paclitaxel).

Of the 23 patients, 4 (17.4%) received six cycles of treatment. Withdrawals included 11 patients (47.8%) due to disease progression, two patients from dose level 6 due to treatment-related adverse events (leucopenia and thrombocytopenia, respectively), a further patient from dose level 6 due to oesophagitis and respiratory disorder, one patient from dose level 1 because of paralysis (Brown-Sequard's syndrome), and four patients because of clinical deterioration.

Pharmacokinetics

The pharmacokinetic results from cycle 1 are shown in Table 4. Platinum levels in ultrafiltrate, expressed both as Cmax and AUC, increased with the dose of ZD0473; the same pattern was seen in plasma (data not shown). There was no apparent effect of paclitaxel dose on platinum kinetics. The elimination half-lives of platinum in plasma and ultrafiltrate (120 h and 80 h, respectively) were consistent across dose levels and consistent with the values found in previous monotherapy studies. A high degree of variability in paclitaxel exposure was noted across the dose levels and it was not possible to assess any effect of ZD0473 on paclitaxel kinetics.

Antitumour activity

Of the 23 patients treated, 11 (47.8%) had a best objective response of stable disease, 10 (43.5%) had disease progression, one (4.3%) had symptomatic deterioration, and one (4.3%) was not evaluable. Of the 11 patients with stable disease, 4 had a ≥25% reduction in tumour size at some point before progression. All four of these patients had NSCLC; two each were treated at dose levels 1 and 6.

Discussion

This is the first clinical study in which ZD0473 in combination with paclitaxel has been evaluated. This combination showed a manageable and predictable tolerability profile in patients with a range of refractory solid malignancies. The DLT was myelosuppression (thrombocytopenia) and other adverse events were generally mild-to-moderate. Importantly, there was no evidence of cumulative toxicity, and this combination did not cause clinically significant nephro-, neuro- or ototoxicity. There was evidence of activity in the form of disease stabilization in almost half of the patients treated, including tumour shrinkage in four patients with NSCLC. No obvious pharmacokinetic interaction between ZD0473 and paclitaxel was detected.

In phase I trials of cisplatin or carboplatin combined with paclitaxel in patients who had pretreated advanced solid tumours [4] or untreated NSCLC [1, 11, 12, 13], the paclitaxel doses at which the MTD was reached were similar to those seen in the present study, ranging between 185 and 235 mg/m^2. The main toxicities with cisplatin/carboplatin plus paclitaxel combinations were

Table 2 Patient exposure to study treatment

Dose level ZD0473/paclitaxel (mg/m^2)	Number of cycles		Cycles received	
	Mean (range)	Total	One to three	Four to six
1: 60/135 ($n=4$)	4 (1–6)	15	1	3
2: 90/135 ($n=3$)	2 (1–6)	9	2	1
3: 120/135 ($n=3$)	4 (2–6)	12	1	2
4: 120/150 ($n=3$)	4 (3–4)	11	1	2
5: 120/175 ($n=4$)	2 (2–4)	10	3	1
6: 150/175 ($n=6$)	3 (1–6)	19	4	2
All ($n=23$)	3 (1–6)	76	12	11

Table 3 Most common grade 3/4 haematological and non-haematological toxicities (all cycles), irrespective of causality

Dose leve ZD0473/paclitaxel (mg/m^2)	Haematological				Non-haematological			
	Anaemia	Leucopenia	Neutropenia	Thrombocytopenia[a]	Alopecia	Pleural effusion	Somnolence	Vomiting
1: 60/135 ($n=4$)	0	1	1	0	1	0	0	0
2: 90/135 ($n=3$)	0	0	1	0	0	2	0	0
3: 120/135 ($n=3$)	1	2	2	1	0	0	1	0
4: 120/150 ($n=3$)	1	1	1	1	1	1	1	0
5: 120/175 ($n=4$)	0	1	1	1	0	0	0	1
6: 150/175 ($n=6$)	3	3	3	5	1	0	0	1
All (%) ($n=23$)	5 (21.7)	8 (34.8)	9 (39.1)	8 (34.8)	3 (13.0)	3 (13.0)	2 (8.7)	2 (8.7)

[a]The CTC definition of grade 4 thrombocytopenia is platelets $<10\times10^9$/l, but in this study, the dose-limiting value was platelets $<25\times10^9$/l

Table 4 Pharmacokinetic data cycle 1 (mean values and coefficient of variation %) (*NC* not calculated as full data set available for only one patient)

Dose level ZD0473/paclitaxel (mg/m^2)	Platinum (ultrafiltrate)			Paclitaxel		
	Cmax (ng/ml)	AUC (ng·h/ml)	CL (l/h)	Cmax (ng/ml)	AUC (ng·h/ml)	CL (l/h)
1: 60/135	1050 (46%)	NC	NC	1510 (39%)	6,000 (65%)	40.5 (67%)
2: 90/135	NC	NC	NC	2540 (69%)	10,000 (33%)	22.5 (26%)
3: 120/135	1830 (19%)	12,500 (31%)	18.5 (39%)	2230 (54%)	12,100 (65%)	21.0 (72%)
4: 120/150	1950 (20%)	14,200 (49%)	15.2 (51%)	1900 (28%)	8,320 (22%)	32 (24%)
5: 120/174	2370 (28%)	9,410 (26%)	21.0 (27%)	1670 (88%)	9,500 (74%)	31 (67%)
6: 150/175	2350 (17%)	20,000 (46%)	31.8 (59%)	2220 (73%)	9,790 (40%)	33 (28%)

similar to those seen in the current study, but in addition, neurotoxicity occurred with cisplatin and carboplatin, especially after cisplatin therapy in platinum-pretreated patients [4, 11].

Reported objective response rates in the phase I studies of cisplatin/carboplatin plus paclitaxel combinations in patients with untreated NSCLC are higher than those in the present study, ranging between 27% and 50% [1, 11, 12, 13]. However, in the present study a range of dose levels were utilized and patients predominantly had pretreated NSCLC or mesothelioma, so a lower level of response may be expected. In a phase I study of cisplatin plus paclitaxel in a range of advanced solid tumours, the overall response rate in patients pretreated with chemotherapy was 20% [4]. However, in contrast to the present study, the use of granulocyte colony-stimulating factor support in some of the trials [4, 11] allowed higher drug doses to be administered.

Although antitumour activity was a secondary endpoint and patient numbers were small, paclitaxel followed by ZD0473 appears no more effective in the treatment of advanced, solid refractory tumours than current platinum-based combination regimens. Therefore, tolerability of the apparent RD of ZD0473 combined with paclitaxel was not confirmed in an expanded cohort of patients. Interestingly, a recently reported preclinical study suggests that the sequence of ZD0473 followed by paclitaxel may be synergistic, but not the reverse sequence as used in the current study [9].

In conclusion, ZD0473 combined with paclitaxel has a manageable tolerability profile in a range of solid, refractory tumours. ZD0473 combination regimens may have a more manageable toxicity profile than other platinum-based combinations, particularly those containing cisplatin. Should further monotherapy trials indicate that ZD0473 has greater efficacy than carboplatin, additional trials of ZD0473 in combination with paclitaxel may be warranted. Using this schedule, paclitaxel 175 mg/m^2 followed by ZD0473 120 mg/m^2 appears to be the RD, but evaluation in additional trials of the reverse sequence of administration may be recommended.

References

1. Belani CP, Kearns CM, Zuhowski EG, Erkmen K, Hiponia D, Zacharski D, Engstrom C, Ramanathan RK, Capozzoli MJ, Aisner J, Egorin MJ (1999) Phase I trial, including pharmacokinetic and pharmacodynamic correlations of combination paclitaxel and carboplatin in patients with metastatic non-small-cell lung cancer. J Clin Oncol 17:676–684
2. Chabner BA, Horowitz SB, Clendennin NJ, Purvis JD (1991) Vinca alkaloids. Cancer Chemother Biol Response Modif 12:67–73
3. du Bois A (2001) Treatment of advanced ovarian cancer. Eur J Cancer 37 [Suppl 9]:S1–7
4. Frasci G, Comella P, Parziale A, Casaretti R, Daponte A, Gravina A, De Rosa L, Gallipoli A, Comella G (1997) Cisplatin-paclitaxel weekly schedule in advanced solid tumours: a phase I study. Ann Oncol 8:291–293

5. Gore M, Atkinson RJ, Dirix L, Rischin D, Beale P, Harnet P, Hacking D, Cure H, Cosaert J (2001) ZD0473 phase II monotherapy trial in second-line ovarian cancer (abstract 967). Eur J Cancer 37 [Suppl 6):S261
6. Hoctin-Boes G, Cosaert J, Koehler M, Smith M (2001) Safety profile of ZD0473 in phase II trials of patients with advanced cancers (abstract 1372). Proc Am Soc Clin Oncol 20:344
7. O'Dwyer PJ, Stevenson JP, Johnson SW (2000) Clinical pharmacokinetics and administration of established platinum drugs. Drugs 59 [Suppl 4]:19–27
8. Perez RP (1998) Cellular and molecular determinants of cisplatin resistance. Eur J Cancer 34:1535–1542
9. Rogers PM, Boxall F, Allott CP, Stephens TC, Kelland LR (2002) Sequence-dependent synergism between the new generation platinum agent ZD0473 and paclitaxel in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. Eur J Cancer 38:1653–1660
10. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247–1259
11. Rowinsky EK, Flood WA, Sartorius SE, Bowling KM, Ettinger DS (1997) Phase I study of paclitaxel on a 3-hour schedule followed by carboplatin in untreated patients with stage IV non-small cell lung cancer. Invest New Drugs 15:129–138
12. Scagliotti GV, Crino L, Pozzi E, Corgna E, Palladino M, Masiero P, Salsano V, Gentile A, Tonato M (1996) Preliminary results of a dose-finding study of paclitaxel and carboplatin in patients with advanced non-small cell lung cancer. Semin Oncol 23 [6 Suppl 16]:80–83
13. Scagliotti GV, Crino L, Pozzi E, Corgna E, Selvaggi G, Novello S, Salsano G, Gentile A, Palladino M, Marracolo F, Tonato M (1999) Phase I/II dose finding study of paclitaxel and carboplatin in advanced non-small cell lung cancer. Lung Cancer 25:39–46
14. Schiller J (2001) Current standards of care in small-cell and non-small cell lung cancer. Oncology 61 [Suppl 1]:3–13
15. Schiller J, Bonomi P, Modiano M, Cornett P, Koehler M (2001) Activity of ZD0473 in small-cell lung cancer: an update in patients relapsing after one prior chemotherapy regimen (abstract 219). Eur J Cancer 37 [Suppl 6]:S62
16. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216