

A phase I study of AMD473 and docetaxel given once every 3 weeks in patients with advanced refractory cancer: a National Cancer Institute of Canada-Clinical Trials Group trial, IND 131

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Background: AMD473 (previously ZD0473) is a new-generation platinum compound with activity against a wide range of human tumour cell lines and xenografts, including carboplatin- and cisplatin-resistant lines. To assess its potential combined with a taxane, a phase I study of AMD473 and docetaxel in advanced cancer was initiated by the National Cancer Institute of Canada-Clinical Trials Group.

Patients and methods: Patients with advanced cancer, measurable disease, performance status Eastern Cooperative Oncology Group 0–2, no major organ dysfunction, and one or no previous taxane regimen received escalating doses of AMD473 and docetaxel every 3 weeks, with a starting dose of AMD473 80 mg/m² and docetaxel 60 mg/m².

Results: Thirty-three patients enrolled on four dose levels were evaluable for toxicity and 25 patients were evaluable for response. The maximum tolerated dose was dose level 4 (AMD473 120 mg/m² and docetaxel 75 mg/m²), with grade 4 neutropenia in both minimally and heavily pre-treated patients causing dose-limiting toxicity. As well at dose level 4, one patient had grade 3 vomiting despite premedication. Dose level three was expanded for both groups of patients and was defined as the recommended phase II dose at AMD473 100 mg/m² and docetaxel 75 mg/m². Non-hematologic toxicities included fatigue, diarrhoea and other mild toxicities. There was one partial response in a patient with prostate cancer and stable disease in 15 patients. No apparent pharmacokinetic interaction was noted.

Conclusion: AMD473 and docetaxel can be combined with a recommended phase II dose level of 100 mg/m² and 75 mg/m², respectively, given intravenously every 3 weeks. The combination has activity and should be explored in responsive tumour types.

Key words: AMD473, docetaxel, phase I studies

Introduction

Platinum agents have broad activity in a wide variety of malignancies, including testicular, ovarian, lung, breast, bladder and other tumour types [1]. Cisplatin, the first platinum analogue, was introduced ~20 years ago and is still widely used despite its troublesome neurotoxicity and nephrotoxicity [2]. Subsequently, carboplatin was introduced and found to

have significant activity and a different spectrum of toxicity, substituting myelosuppression as its dose-limiting toxicity (DLT) [3–7]. The efficacy of the platinum analogues is limited by several (intrinsic and acquired) mechanisms of resistance, including impaired cellular uptake, intracellular inactivation by thiols [e.g. reduced glutathione (GSH)] and enhanced DNA repair.

AMD473 (previously known as ZD0473, and now called AMD473 again) is a new platinum analogue that was specifically developed to overcome acquired platinum resistance, in particular detoxification by intracellular thiols [8]. It appears to have a different DNA sequence specificity compared with cisplatin and circumvents acquired resistance mediated by

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changes in uptake and retention, DNA repair and GSH uptake [9]. Like other platinum analogues, AMD473 causes cell death by the formation of covalent cross-links that interfere with DNA replication and transcription, and lead to cell death [10]. However, AMD473 forms cross-links at a rate intermediate to that of cisplatin and carboplatin, and a novel pattern of DNA binding was identified with AMD473 in pBR322 DNA [9]. AMD473 was tested against a panel of 11 human ovarian carcinoma cell lines, including cell lines with acquired resistance to cisplatin in culture [9]. Across these 11 cell lines, AMD473 exhibited intermediate potency compared with cisplatin and carboplatin against sensitive cell lines (41M, CH1 and A2780) and showed similar potency to carboplatin. The data demonstrated that AMD473 retained activity in the three cell line pairs where the mechanisms of resistance were variable, including that due to reduced drug uptake in the 41McisR, enhanced DNA repair in the CH1cisR, and uptake, repair and increased glutathione levels in the A2780cisR. AMD473 was tested in other cell lines, including colorectal cancer and breast cancer, and found to be active [8, 10–13]. Pearson coefficient compare analysis resulting from *in vitro* data using the National Cancer Institute 60 cell line panel indicated that AMD473 did not share a response pattern with any other agent in the databank [9]. Antitumour activity was observed in several tumour models, including ovarian xenograft models with acquired resistance to cisplatin (CH1cisR) and carboplatin (HX110P), and improved efficacy in head to head experiments compared with cisplatin and satraplatin [13].

Phase I studies of AMD473 defined a maximum tolerated dose (MTD) of 150 mg/m² when administered as a 2–3 h infusion every 4 weeks, with a DLT of thrombocytopenia and febrile neutropenia [14]. Other toxicities were mild and nephrotoxicity was unusual. Pharmacokinetics showed a linear relationship between dose and myelosuppression. The trial also suggested that patients who were less heavily pretreated tolerated 150 mg/m² without excessive toxicity. The recommended phase II dose (RP2D) was 120 mg/m², with escalation to 150 mg/m² in the absence of toxicity, given every 3 weeks. Phase II studies suggested activity and confirmed this dose [15–21].

Taxanes, including both paclitaxel and docetaxel, are commonly used in combination with platinum agents and in recent years these couplets have become the mainstay of therapies for ovarian, lung and other common tumour types [22–27]. Although active, these couplets are associated with a high risk of recurrence and significant toxicity. Combinations of a taxane with a platinum analogue that may be more active or active in resistant tumours continues to be of interest. Preclinical studies suggested synergy with AMD473 and paclitaxel. Also, sequence-dependent synergism between the new-generation platinum agent AMD473 and paclitaxel was shown in both cisplatin-sensitive and -resistant human ovarian carcinoma cell lines [28]. Finally, AMD473 may have potential as an oral platinum agent. With these data and the potential of using AMD473 in a wide variety of tumour types that may be resistant to other platinum agents, the National Cancer

Institute of Canada-Clinical Trials Group (NCIC-CTG) initiated a two-centre, dose-escalating phase I study of AMD473 in combination with docetaxel in patients with advanced cancer.

Patients and methods

This was a non-randomized, dose seeking, open label, combination phase I trial. Eligible patients had documented evidence of advanced cancer that was refractory to or incurable by standard therapy, with at least one disease site that could be measured by X-ray, conventional computed tomography (CT) scan or physical examination at ≥ 20 mm, or by spiral CT scan at ≥ 10 mm. They also had to be ≥ 18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a maximum of two previous chemotherapy regimens with no more than one previous taxane-containing regimen, and have provided written informed consent. Previous radiation had to have included no more than 30% of functioning bone marrow. Laboratory eligibility was defined as follows: adequate hematological function (absolute granulocyte count $\geq 1.5 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$); adequate chemistry [serum creatinine less than or equal to the upper normal limit (UNL) or creatinine clearance ≥ 60 ml/min based on the Cockcroft–Gault formula]; bilirubin \leq UNL, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and alkaline phosphatase $\leq 2 \times$ UNL [29]. Patients who were pregnant, not using adequate contraceptive precautions, had newly diagnosed brain metastases, who were on other experimental agents, had neurotoxicity or pre-existing neuropathies grade ≥ 3 , or had other significant medical or psychiatric conditions were not eligible. There was a requirement for at least 3 weeks to have elapsed since previous radiotherapy, surgery or chemotherapy.

All patients were assessed at baseline with a history, physical examination, hematology and chemistry panel, diagnostic imaging of their disease and a baseline toxicity assessment before being enrolled with the NCIC-CTG central office.

Patients in the initial cohort were treated with an intravenous infusion of docetaxel 60 mg/m² followed by AMD473 80 mg/m², with each administered over 60 min. As AMD473 is a platinum compound and known to be emetogenic, the prophylactic use of anti-emetics including 5HT₃ antagonists was recommended. Actual weights were used for body surface area calculations.

Cohorts of three patients per dose level were planned with recommendations for expansion of the cohorts if toxicity was seen to maintain adequate numbers of evaluable patients. The initial definitions only provided grading for toxicity, and after the initial cohort the protocol was amended to allow for duration of grade 4 granulocytopenia. The amended criteria are as follows. DLT was defined as any of the following occurring within cycle one: absolute granulocyte count (AGC) $< 0.5 \times 10^9/l$ for ≥ 7 days; platelets $< 10.0 \times 10^9/l$ or thrombocytopenic bleeding; febrile neutropenia; or grade ≥ 3 non-hematologic toxicity. If two or more patients in a cohort had DLT as defined above, that dose was defined as the MTD; an additional six patients were then to be treated at one dose level below the MTD in order to define the RP2D.

Patients were assessed for toxicity every 3 weeks and for response every second cycle. Treatment was discontinued for progressive disease, unacceptable toxicity, an intercurrent illness that would affect assessments, or if requested by the patient. Treatment was continued in patients with stable disease to a maximum of six cycles. In patients with a partial or complete response (PR or CR, respectively), there was the option to continue therapy until disease progression or until two cycles after the confirmed response. Patients with progressive disease were to go off study at the time of documentation of progression. All patients were seen 4 weeks and then 3 months after completion of the protocol therapy.

Response was defined by the RECIST (response evaluation criteria in solid tumours) criteria [30]. The response duration was the time that CR or PR was first achieved to the first date of progressive disease. Stable disease duration was the time from the start of therapy to the date of progression.

Pharmacokinetics

The pharmacokinetics of both the AMD473 and the docetaxel were assessed during the first 2 weeks of cycle 1 in all patients entered at a dose level. For the total platinum analysis, 9-ml blood samples were collected in lithium heparin tubes and centrifuged within 10–15 min for 10 min so that a 1 ml aliquot of plasma could be stored in plain polypropylene tubes. The remainder of the plasma was centrifuged for 45 min and stored in a similar manner as the other aliquots at -70°C .

Pharmacokinetics samples for AMD473 were collected during cycle 1 at the following time points: before the infusion, at the end of the infusion, 2, 4, 6, and 24 h after the infusion, and at 5, 8 and 15 days following completion of the infusion. For the docetaxel analysis, 5 ml blood samples were collected and centrifuged for 10 min and stored in a plain tube at -20°C . Samples were collected for docetaxel cycle 1 before the beginning of the infusion, at the end of the infusion, and at 15 min and 1, 2, 4, 6, 8 and 24 h following completion of the infusion.

Plasma and plasma ultrafiltrate (PUF) were analysed for platinum from AMD473 by Covance Laboratories Ltd, without predigestion by atomic absorption spectrophotometry against a matrix-matched standard solution. Peak area absorbance values were obtained from a graphite furnace equipped with Zeeman background correction. All samples were analysed individually. Docetaxel levels were determined in human plasma using a method previously validated at BAS Analytics Ltd. Two sets of calibration standards were included in each analysis batch of docetaxel, and standard curves were constructed by performing linear regression analysis weighted to $1/x^2$.

Statistical plan

The primary objective of the trial was to determine the recommended doses of docetaxel and AMD473 when given in combination, with the end points of safety and tolerability. Objective response was a secondary end point. The sample size was determined by the number of patients required to reach the MTD. Toxicities were monitored on an ongoing basis, with all events described [31].

Results

Patients and administered doses

Thirty-three patients were enrolled from two cancer centres between May 2000 and February 2002. The dose levels and the numbers of patients per level are summarized in Table 1. All were evaluable for toxicity and 25 were evaluable for response. Reasons for not being evaluable for response included non-measurable disease in four patients and disease not being reassessed in four patients. A total of 123 cycles of therapy over four escalating dose levels were assessed. The number of cycles ranged from one to eight. A total of 21 patients received three or more cycles of chemotherapy on trial, with two patients at dose level one and one patient at dose level 2, receiving eight cycles of combined therapy.

Patient characteristics are summarized in Table 2. A variety of malignancies were represented. Median age was 60 years (range 45–77 years). Fifteen of the patients were female. Only

Table 1. Starting doses, and numbers of patients and cycles

Dose	Starting dose (AMD473 mg/m ²)/ (docetaxel mg/m ²)	No. of patients	Total no. of cycles	Median no. of cycles (range)	No. of DLTs
1	80/60	8	44	6 (1–8)	1
2	80/75	6	26	4 (2–8)	1
3	100/75	9	24	2 (1–4)	2 ^a
4	120/75	10	29	3 (1–6)	3 ^b

^aTwo of two patients with DLT were heavily pretreated.

^bTwo of three patients with DLT were heavily pretreated.

DLT, dose-limiting toxicity.

Table 2. Patient characteristics ($n=33$)

Age, years	
Median	60
Range	45–77
No. of patients	
Female/male	15/18
Performance status (ECOG)	
0	24
4	5
Malignancy type	
Non-small-cell lung cancer	11
Small-cell lung cancer	4
Head and neck cancer	3
Prostate	3
Renal cell	2
Oesophageal	2
Bladder, breast, colon, endometrial, ovary, pancreas, rectal, sarcoma, unknown primary	1 each
Previous therapy	
Adjuvant/neoadjuvant	6
Metastatic chemotherapy	28
Radiation	23
Number of previous chemotherapy regimens	
0	14
3	15
Number of disease sites	
1	9
2	9
3	8
≥ 4	7
Histology	
Squamous	9
Adenocarcinoma	8
Undifferentiated	6
Infiltrating ductal	1
Clear cell	1
Missing/unknown/other	8

ECOG, Eastern Cooperative Oncology Group.

three patients had received no previous chemotherapy. Fourteen patients had received one previous regimen, 15 patients had received two, and one patient had three prior chemotherapy regimens. Eight and 19 of the patients had received previous

Table 3. Non-hematologic toxicity possibly, probably or definitely related to AMD473 and docetaxel (worst by starting dose by patient)

Toxicity	Dose level									
	1 (n=8)		2 (n=6)			3 (n=9)			4 (n=10)	
	Grade		Grade			Grade			Grade	
	3	4	3	4	5	3	4	5	3	4
Fatigue	1	–	1	–	–	1	–	–	2	–
Febrile neutropenia	–	–	1	–	1	2	–	–	2	–
Infection with ANCN	1	–	–	–	–	–	1	–	1	1
Vomiting	–	–	1	–	–	–	–	–	1	–
Diarrhoea	1	–	–	–	–	3	–	–	–	–
Melena/GI bleed	1	–	–	–	–	–	–	–	–	–
Confusion	–	–	–	–	–	1	–	–	–	–
LOC decrease	–	–	–	–	–	1	–	–	–	–
Dyspnea	–	–	–	–	–	–	1	–	–	–
Neuropathy-sensory	–	–	–	–	–	–	–	1	–	–

ANCn, ANC normal; GI, gastrointestinal; LOC, level of consciousness.

taxane therapy and platinum exposure, respectively. Nine patients had only one site of disease, nine had two sites, eight had three sites and seven had four or more sites.

Dose reductions and delays

A total of seven patients received dose reductions during the trial. Docetaxel dose was reduced in four patients: three due to hematologic toxicity and the other at the investigator's discretion. AMD473 dose was reduced in five patients: three due to hematologic toxicity and two at the investigator's request. Six patients had the delivery of AMD473 delayed at least once: two due to hematologic toxicity and four because of statutory holidays or patient request.

Toxicity

Dose-limiting toxicity. DLT defined the number of patients in each cohort. Table 3 summarizes related grade 3 and 4 non-hematological toxicities at all dose levels. Four patients were initially accrued at the first dose level of AMD473 80 mg/m² and docetaxel 60 mg/m². Of the three patients evaluable for hematological toxicity, all experienced grade 4 granulocytopenia, including one patient who had granulocytopenia for >4 days and then received granulocyte colony-stimulating factor. This dose level was expanded to a total of eight patients, yielding six evaluable patients, and the protocol was amended to define a DLT as ≥7 days of grade 4 AGC. At the second dose level, after one patient was hospitalized for febrile neutropenia, this dose level was expanded with an additional two patients. There were no further DLT in this cohort and dose escalation continued. At dose level 4 (AMD473 120 mg/m² and docetaxel 75 mg/m²) all three initial patients had grade 4 neutropenia, with one patient experiencing DLT (febrile neu-

tropenia). This dose level was therefore expanded and an additional four patients were enrolled. One of these patients had a DLT with febrile neutropenia and another experienced prolonged grade 4 neutropenia (≥7 days) in all but the first cycle of treatment, so it was therefore also considered a DLT. Of the three patients at dose level 4 with DLTs, two were considered to be heavily pretreated with previous pelvic irradiation and/or two previous chemotherapy regimens. Thus, dose level 4 was defined as the MTD for heavily pretreated patients. Additional heavily pretreated patients were enrolled at dose level 3. In the cohort of heavily pretreated patients at dose level 3, one patient had a DLT with grade 3 confusion, depressed level of consciousness (LOC), and pneumonia with grade 3 neutropenia, ultimately resulting in death. In an expanded cohort of heavily pretreated patients at this dose level, one patient had grade 3 diarrhoea, possibly related to the study drug, and therefore two out of nine patients at this dose level experienced a DLT. This dose was therefore also defined as the RP2D for heavily pretreated patients.

Additional minimally pretreated patients (no previous pelvic radiation, 0–1 previous chemotherapy regimens) were enrolled on the top dose level (4). Two of the three minimally treated patients at dose level 4 experienced a DLT, one experiencing a neutropenic infection and one with grade 3 vomiting despite premedication. Dose level 4 was therefore defined as the MTD for both minimally and heavily pretreated patients. As none of the minimally pretreated patients had experienced a DLT at dose level 3, it was defined as the RP2D for minimally pretreated patients.

Toxicity. Table 3 summarizes the non-hematologic toxicity (grade ≥3) seen at each dose level that was thought to be possibly, probably or definitely related to the protocol treatment and that was seen at all cycles (not just cycle 1 where the DLTs were defined). The major grade 3 toxicity was

Table 4. Hematologic toxicity worst by starting dose by patient (all cycles)

Starting dose	Evaluable patients	Grade				
		0	1	2	3	4
1 (AMD473 80 mg/m ² + Doc 60 mg/m ²)						
Granulocytes	8	–	–	2	1	5
Haemoglobin	8	–	3	1	4	–
Platelets	8	4	1	2	1	–
WBC	8	–	–	3	3	2
2 (AMD473 80 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	6	–	–	1	–	5
Haemoglobin	6	–	2	4	–	–
Platelets	6	4	1	–	1	–
WBC	6	–	1	–	3	2
3 (AMD473 100 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	9	1	–	–	2	6
Haemoglobin	9	–	3	3	3	–
Platelets	9	4	2	2	1	–
WBC	9	–	1	1	2	5
4 (AMD473 120 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	10	–	–	–	1	9
Haemoglobin	10	–	1	8	1	–
Platelets	10	3	5	1	1	–
WBC	10	–	–	1	4	5

Doc, docetaxel; WBC, white blood cells.

fatigue, which was seen in one patient at dose levels 1–3, as well as in two patients at dose level 4. Two other episodes of grade 3 toxicity were seen at dose level 1, with one melena/gastrointestinal bleed and one neutropenic infection. At dose levels 2 and 4, one episode of grade 3 vomiting was seen. Grade 3 diarrhoea was seen in one patient at dose level 1, and in three patients at dose level 3. One episode each of grade 3 confusion and depressed LOC (in a dose level 3 patient) was possibly related to the protocol treatment. One grade 5 neutropenic infection was reported at dose level 4. Grade 4 dyspnea was reported at the third dose level in one patient.

Mild toxicity was typical of the expected toxicities reported with this drug. Alopecia was not universal. Mild oedema was seen in six instances and was grade 1 in all but two cases (one in each of the lower dose levels). Seventeen patients had stomatitis, all grades 1 and 2.

Biochemical toxicity was minimal. When the patients with normal baseline counts were assessed there was a grade 2 rise in creatinine and a similar rise in AST seen at dose level 3. No other rises greater than grade 1 were seen at any of the dose levels and no pattern of change was apparent for the mild rises. When patients with abnormal baselines were assessed, there were two additional grade 2 rises, one in alkaline phosphatase at dose level 1 and one in AST at dose level 2.

Table 5. Hematologic toxicity worst by starting dose by patient (cycle 1 only including DLTs)

Starting dose	Evaluable patients	Grade				
		0	1	2	3	4
1 (AMD473 80 mg/m ² + Doc 60 mg/m ²)						
Granulocytes	7	1	–	–	1	5
Haemoglobin	7	–	4	2	1	–
Platelets	7	6	1	–	–	–
WBC	7	1	–	2	3	1
2 (AMD473 80 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	5	–	–	2	–	3
Haemoglobin	5	–	3	2	–	–
Platelets	5	4	1	–	–	–
WBC	5	–	1	1	2	1
3 (AMD473 100 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	9	2	–	1	2	4
Haemoglobin	9	–	4	4	1	–
Platelets	9	6	3	–	–	–
WBC	9	1	1	2	2	3
4 (AMD473 120 mg/m ² + Doc 75 mg/m ²)						
Granulocytes	10	1	–	1	1	7
Haemoglobin	10	1	3	5	1	–
Platelets	10	6	2	1	1	–
WBC	10	1	1	–	5	3

Doc, docetaxel; WBC, white blood cells.

Hematologic toxicity. Hematologic toxicity was the major DLT, and predominantly consisted of neutropenia. Tables 4 and 5 summarize the toxicity that was seen at all doses, by both the starting dose of the patient and by the first cycle. The median nadir of the granulocyte count for all cycles was 0.10 for the top dose (range 0.00–0.50). At the other doses the median nadir varied from 0.10 to 0.30 (ranges 0.00–2.30). The number of days to the nadir granulocyte count was 31 days for dose level 3 and 20 days for dose level 4 (ranges 8–72 days and 8–52 days, respectively). Although the lower end of the range was similar for the two lower dose levels, the median was higher at 41 days each (range 9–78 days).

Response

Twenty-five patients were assessable for response. One partial response occurred in a patient with prostate cancer who had received no previous cytotoxic chemotherapy (duration of response 7.2 months). Fifteen patients had stable disease and nine had progressive disease. The median duration for stable disease was 3.0 months (range 1.4–15.2 months).

Pharmacokinetics

Plasma and PUF were assessed for AMD473 at nine time points in 33 patients. There was no apparent interaction seen

Table 6. Pharmacokinetics of AMD473 and docetaxel in plasma

Drug dose (mg/m ² /day)	AUC inf. (mg·h/l)	Vol. dist. (l)	Clearance (l/h)	Half-life (h)
Docetaxel				
AMD473 80 mg/m ² + Doc 60 mg/m ²				
<i>n</i>	8	8	8	8
Mean	2.48	357.89	77.09	9.13
SEM	0.99	135.44	15.41	2.96
AMD473 80 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	6	6	6	6
Mean	2.24	262.27	65.48	8.32
SEM	0.38	88.04	13.01	3.20
AMD473 100 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	9	9	9	9
Mean	2.55	192.54	60.85	8.05
SEM	0.34	51.55	9.05	2.14
AMD473 120 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	10	10	10	10
Mean	2.30	380.43	67.91	10.68
SEM	0.25	117.80	9.30	2.45
AMD473				
AMD473 80 mg/m ² + Doc 60 mg/m ²				
<i>n</i>	8	8	8	8
Mean	164.08	191.84	0.92	157.07
SEM	9.58	10.85	0.06	7.88
AMD473 80 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	6	6	6	6
Mean	187.39	160.94	0.71	170.51
SEM	12.68	12.37	0.06	13.84
AMD473 100 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	9	9	9	9
Mean	219.69	174.80	0.83	159.56
SEM	13.74	12.94	0.08	7.30
AMD473 120 mg/m ² + Doc 75 mg/m ²				
<i>n</i>	10	10	10	10
Mean	239.76	182.91	0.95	144.25
SEM	14.94	15.67	0.08	9.81

AUC inf., AUC infusion; Vol. dist., volume of distribution; Doc, docetaxel; SEM, standard error of the mean.

between AMD473 and docetaxel based on our findings and a comparison of the published literature on single-agent administration. The docetaxel AUC (area under the curve for drug concentration as a function of time) was assessed for the two doses of 60 and 75 mg/m², and was 2.48 mg·h/l for the lower dose, with a range between 2.24 and 2.55 mg·h/l for the higher dose. Table 6 shows these data with the means and standard errors of the mean, as well as the number of patients in each cohort. Plasma values are shown as they were available for both drugs. The volume of distribution and clearance

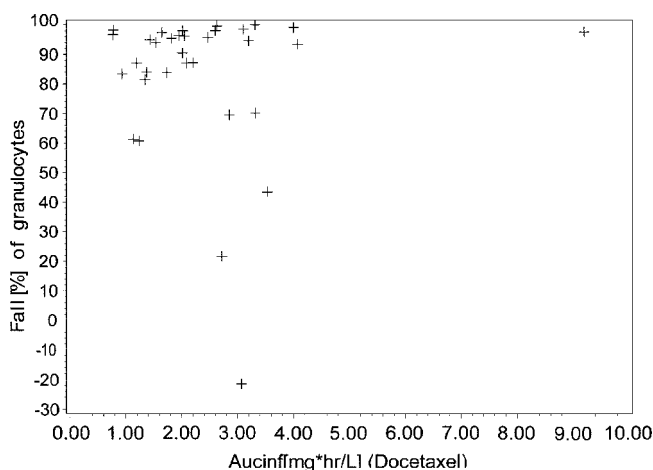


Figure 1. Plot of the individual patient's granulocyte count against the AUC (area under the curve) of docetaxel. Fall in patient's granulocyte count versus individual AUC of docetaxel ($r=0.13269$; $P=0.4617$).

for docetaxel had a large standard error and did not relate to the two doses studied. The half-life was a mean of 9.13 h for the lower dose, and between 8.05 and 10.68 h for the higher dose.

AMD473 had an AUC that appeared to rise with increasing dose, with a mean of 164.08–187.39 mg·h/l at 80 mg/m² rising to 219.69 mg·h/l at 100 mg/m², and 239.76 mg·h/l for the highest dose of 120 mg/m². These data are shown in Table 6. The volume of distribution, clearance and half-life did not appear to increase with increasing dose, with a half-life between 144 and 170 h.

When the fall in granulocyte count was plotted against the AUC for docetaxel, no consistent relationship was seen, as shown in Figure 1. Although granulocytopenia was seen and was the DLT for the doses studied, there was no direct relationship with the individual patients' AUC and their granulocyte count.

Discussion

There is a need to identify new agents for the treatment of solid tumours. As the combination of a taxane and platinum agent has shown beneficial activity in a wide range of malignancies, new analogues may hold promise in terms of improved efficacy or toxicity profiles. AMD473 showed significant preclinical activity in resistant cell lines and a favourable toxicity profile.

In this trial of AMD473 and docetaxel given every 3 weeks, the DLT was hematological, with both myelosuppression and thrombocytopenia. Grade 3 diarrhoea was also a DLT at the highest dose. Although initially it appeared that patients who were heavily pretreated were experiencing more toxicity, when additional patients were enrolled to explore this possibility a difference in the toxicity between the two groups was not readily apparent. The RP2D for both the minimally and heavily pretreated patients in this study was AMD473 100 mg/m² and docetaxel 75 mg/m², each given over 60 min every 3 weeks.

The patient population included a number of heavily pre-treated patients, and by definition and eligibility those included had malignancies that were refractory to standard therapy or for whom no curable therapy was available. Also, 15 patients had previous exposure to a platinum agent and eight to a taxane, and therefore would be expected to have a lower probability of responding to this combination. However, despite this population we did see biological activity with this combination with one partial response, and an additional 15 patients or 60% of the 25 evaluable patients having stable disease. Combinations of carboplatin–docetaxel, oxaloplatin–docetaxel, carboplatin–paclitaxel and other platinum–taxane couplets have been reported in phase II and III studies, with good response rates. In many, enrolment was restricted to chemotherapy-naïve patients. We cannot adequately compare the docetaxel–AMD473 couplet with other platinum–taxane combinations studied in a more favourable patient population, but our results suggest that this combination may be worthy of further study in potentially sensitive tumours.

The lack of nephrotoxicity and neurotoxicity clearly differentiates this couplet from combinations containing cisplatin. Certainly it is those toxicities that restrict the use of cisplatin-containing combinations in many clinical settings, and a drug without these complications may have a role in combination chemotherapy.

The pharmacokinetics did not show any interaction between AMD473 and docetaxel, which is important with respect to the future utility of this combination. The pharmacokinetics of AMD473 and docetaxel observed in this study were consistent with the data observed in other trials, where AMD473 was administered as a single agent [14, 18]. In the limited range of doses studied, there was very little difference in the levels of AUC, clearance and half-life. Also, when AUC was plotted against granulocyte count nadir, no relationship was seen. This suggests that there will not be wide variability and unpredictable individual pharmacogenomic patterns, which may be associated with significant toxicities and concerns about the widespread use of the drug.

The combination of AMD473, a novel platinum agent, and docetaxel showed evidence of activity and had very tolerable toxicity. Future phase II trials of AMD473 in combination with docetaxel in potentially sensitive tumours would be of interest and should be pursued.

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