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A phase II trial of ZD0473 in platinum-pretreated ovarian cancer

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Abstract

The primary aim of this phase II trial was to assess the antitumour activity of ZD0473 in ovarian cancer patients who had failed initial platinum-based therapy. Patients ($n=94$) were classified as either platinum-sensitive ($n=35$) or platinum-resistant ($n=59$) depending on whether they had relapsed or progressed within 26 weeks of completing first-line platinum-based chemotherapy. Patients initially received 120 mg/m^2 ZD0473 as a 1-h intravenous (i.v.) infusion on day 1 of a 3-week cycle. If well tolerated, the dose could be escalated to 150 mg/m^2. Few patients (9%) withdrew because of treatment-related adverse events and no clinically significant oto-, nephro- or neurotoxicity was observed. Objective response rates for platinum-resistant and sensitive patients were 8.3 and 32.4%, respectively, and clinical benefit was observed in 76.5% of the sensitive patients. Median time to progression was 57 and 180 days, and median time to death was 242 and 402 days, for resistant and sensitive patients, respectively. In conclusion, ZD0473 has a manageable toxicity profile and encouraging activity in platinum-sensitive ovarian cancer patients.

Keywords: Ovarian cancer; Platinum; Resistant; Sensitive; ZD0473; Antitumour activity; Tolerability

1. Introduction

Ovarian cancer is among the leading causes of cancer in women, with over 6800 new cases diagnosed each year in the UK [1]. Prognosis is dependent upon the stage of disease, and the 5-year survival rate for advanced disease (stage IIIA-IV) is 30%, compared with 95% for localised disease (stage IA-IB) [2]. The poor overall prognosis of ovarian cancer is further exacerbated by the fact that most women present with advanced disease at diagnosis; at initial diagnosis, 59% of women have stage IIIA-IV disease, compared with 26% with stage IA-IB disease [2]. As a result, ovarian cancer is one of the leading causes of death from cancer in women, accounting for over 4000 deaths a year, which is more than all the other gynaecological cancers combined [1].

The most commonly used first-line chemotherapy regimen for advanced ovarian cancer is cisplatin or carboplatin combined with paclitaxel [3–5]. Despite reasonable initial response rates in previously untreated patients, most patients with advanced disease ultimately relapse due to inherent or acquired platinum resistance [6]. As a result, second-line treatment options are important components of ovarian cancer therapy. Unfortunately, second-line therapy is not curative because of resistance to platinum and other active agents [4]. The development of resistance is often reflected in the length of time between a patient's last platinum-based treatment and relapse (the platinum-free interval), which

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is proportional to the probability of response to further platinum-containing therapy [7–9].

There is a need for novel, better-tolerated chemotherapeutic agents that can circumvent the mechanisms of platinum resistance and extend the therapeutic options available to patients for whom conventional agents are no longer suitable. The new platinum agent ZD0473 (*cis*-amminedichloro [2-methylpyridine] platinum [II]) was designed to overcome platinum-resistance mechanisms. In preclinical studies, ZD0473 has shown evidence of activity in a variety of tumour types, including ovarian cell lines representing the main mechanisms of platinum resistance [10,11] and cells derived from ovarian tumours [12].

In phase I clinical studies, ZD0473 proved to have a manageable toxicity profile with an antitumour activity, including evidence of activity in an ovarian cancer patient [13]. Based on phase I study data, a starting dose of 120 mg/m^2 was recommended for phase II studies [13]. A more detailed review of ZD0473 is provided in the accompanying supplement [14]. Here, we present the results of a phase II study primarily designed to determine the tolerability and response rate of ZD0473 in patients with relapsed platinum-sensitive and-resistant ovarian cancer.

2. Methods

2.1. Patients

The trial was a phase II, open-label, non-comparative, multicentre study in women with histologically- or cytologically-confirmed measurable ovarian cancer who failed first-line platinum-based chemotherapy.

Patients included in the trial were $\geqslant$18 years of age, with a life expectancy of $\geqslant$12 weeks and a World Health Organization (WHO) performance status of 0-2. In addition, patients had an absolute neutrophil count (ANC) of $\geqslant 1.5 \times 10^9$/l, a platelet count of $\geqslant 100 \times 10^9$/l and a haemoglobin concentration of $\geqslant$90g/l. The trial was conducted in accordance with the Declaration of Helsinki, as amended in South Africa (1996). Patients gave informed written consent before entering the trial and approval was obtained from all relevant ethical committees.

For the purposes of this analysis, patients were classified as either platinum-resistant (patients who relapsed or progressed within 26 weeks of completing first-line platinum-based chemotherapy) or platinum-sensitive (patients who relapsed or progressed after 26 weeks of completing first-line platinum-based chemotherapy).

2.2. Treatment

Patients were initially treated with 120 mg/m^2 ZD0473 as a 1-h intravenous (i.v.) infusion on day 1 of a 3-week cycle. In the absence of major toxicity, the dose could be escalated to 150 mg/m^2. The starting dose was later modified to 150 mg/m^2 after a safety review established 120 mg/m^2 to be well tolerated. For further treatment to be given after the first cycle, patients had to have a ANC $\geqslant 1.5 \times 10^9$/l, a platelet count of $\geqslant 100 \times 10^9$/l, serum creatinine and bilirubin of $\leqslant 1.25 \times$ ULN, along with the resolution of any non-haematological toxicities to $<$grade 2. If these criteria were not met by day 28, the ZD0473 dose was reduced in all subsequent cycles, and patients not meeting these criteria by day 43 were withdrawn from the study. Patients who did not experience disease progression could receive up to six treatment cycles.

2.3. Tolerability

Biochemical and haematological assessments were made on days 1, 8, 15 and 22 of each treatment cycle, at withdrawal and 30 days after the last dose. Where there was a dose delay, the measurements were repeated on days 29, 36 and 43. Adverse events were classified using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and were assessed during each treatment cycle and up to 30 days after the last ZD0473 dose.

2.4. Antitumour activity

The revised NCI response evaluation criteria in solid tumours (RECIST) criteria were used to determine tumour responses after treatment cycles 2, 4 and 6, at withdrawal of treatment and during subsequent visits until disease progression occurred.

3. Results

3.1. Patients and treatment

A total of 94 patients were enrolled onto the trial (Table 1); 37% (35/94) were classified as platinum-sensitive and 63% (59/94) as platinum-resistant. A starting dose of ZD0473 120 mg/m^2 was received by 49 patients; 15 were later escalated to 150 mg/m^2 because the starting dose was well tolerated. A total of 45 patients received a starting dose of 150 mg/m^2. In total, 337 cycles of therapy were given and patients received a median of three cycles (range 1–8). Dose reductions occurred in 37% of patients (35/94), and 44% (41/94) of patients had cycles delayed due to toxicity (Table 2).

3.2. Tolerability

The most frequently observed grade 3/4 toxicity was thrombocytopenia, which occurred in 58 (62%)

Table 1
Patient demographic characteristics

		No. patients ($n=94$)
Platinum-		
	sensitive	35
	resistant	59
Median age, years (range)		58 (27–75)
WHO performance status		
	0	50
	1	36
	2	8
Creatinine clearance (ml/s)		
	<1	14
	1—1.32	37
	⩾1.33	43
Metastatic disease		
	Yes	74
	No	20

WHO, World Health Organisation.

Table 2
ZD0473 treatment received

	ZD0473 dose (mg/m^2)			
	120 ($n=34$)	120/150 ($n=15$)	150 ($n=45$)	Total ($n=94$)
Total no. cycles	104	67	106	337
Median no. cycles	2 (1–8)	6 (2–6)	3 (1—6)	3 (1–8)
No. patients receiving ⩾4 cycles	13	10	21	44
No. patients with cycles delayed due to toxicity	10	6	25	41
No. patients with dose reduced	6	8	21	35

patients, with neutropenia and anaemia occurring in 35 (37%) and 33 (35%) patients, respectively (Table 3). Nausea and vomiting were among the most common non-haematological toxicities (Table 4), but were controlled by use of antiemetics such as serotonin antagonists. Other common toxicities included lethargy, abdominal pain and constipation. No clinically significant oto-, nephro- or neurotoxicity was observed.

Where patient withdrawal occurred, it was predominantly due to disease progression (57 patients; 61%). Only 8 patients (9%) withdrew from the trial because of treatment-related adverse events and none of the drug-related adverse events were fatal. 4 patients (4%) died due to cancer within 30 days of coming off study.

Table 3
No. patients with grade 3/4 haematological toxicity, worst grade per patient

	ZD0473 dose (mg/m^2)			
	120 ($n=34$)	120/150 ($n=15$)	150 ($n=45$)	Total ($n=94$)
Thrombocytopenia	13	9	36	58
Neutropenia	11	3	21	35
Anaemia	10	8	15	33

Table 4
No. patients with non-haematological toxicity, worst grade per patient[a]

	No. patients ($n=94$)	
	Grade 1/2	Grade 3/4
Nausea	50	9
Abdominal pain	43	6
Lethargy	37	16
Vomiting	34	11
Constipation	34	6
Diarrhoea	23	0
Dyspnoea	18	4
Anorexia	17	4
Somnolence	16	1
Headache	16	2
Pain	13	2
Fever	12	3

[a] Grades 1–4 occurring in ⩾15% of patients.

3.3. Antitumour activity

For the analysis of activity, data were available for 48 platinum-resistant and 34 platinum-sensitive patients (Table 5). Objective response (OR) rates for the platinum-resistant and platinum-sensitive patients were 8.3% (95% confidence interval (CI) 2.3–20) and 32.4% (95% CI 17.4–50.5) respectively. Similarly, clinical benefit (defined as complete or partial response or stable disease lasting ⩾6 weeks) was observed in 43.8% (95% CI 29.5–58.8) and 76.5% (95% CI 58.8–89.3) of the platinum-resistant and -sensitive patients, respectively. The time to progression (TTP) data show that the platinum-resistant patients appear to exhibit a shorter median TTP with ZD0473 (57 days; 95% CI 49–92) than the platinum-sensitive patients (180 days; 95% CI 98–299). Similarly, the time to death (TTD) data indicate that the platinum-resistant patients had a shorter survival than the sensitive patients, with median TTD of 242 days (95% CI 194–560) and 402 days (95% CI 309–480), respectively.

4. Discussion

This study demonstrates that second-line ZD0473 has a manageable toxicity profile in ovarian cancer patients. ZD0473 did induce some haematological toxicity, but this did not prevent the administration of the planned doses in over half of the study population. Few patients withdrew due to drug-related adverse events and there was no clinically significant nephro-, oto- or neurotoxicity. This

Table 5
Antitumour activity of ZD0473 in platinum-sensitive and platinum-resistant patients

	No. patients ($n=82$)					Median time (days)	
	Evaluable	Complete response	Partial response	Stable disease	Disease progression	To progression	To death
Resistant	48	3	1	17	27[a]	57	242
Sensitive	34	5	6	15	8[a]	180	402

[a] Includes 1 patient with symptomatic deterioration.

compares favourably with other, clinically approved, platinum therapies for recurrent ovarian cancer, such as cisplatin and carboplatin, for which the predominant toxicities are nephro-, oto- and neurotoxicity for cisplatin and myelosuppression for carboplatin with oto- and neurotoxicity developing at higher doses [15,16].

While it is important that an agent is well tolerated, it is vital that a given treatment also exhibits antitumour activity. While re-treatment with conventional platinum-based regimens produces favourable responses in recurrent disease with a median disease-free interval of 26 months [17], similar re-treatment after a very short platinum-free interval can produce OR rates as low as 4% [18]. In this study, the activity of ZD0473 against platinum-sensitive disease (OR in 32.4% of patients) appears to be broadly equivalent to OR rates reported for other platinum agents in ovarian cancer patients with long platinum-free intervals. For example, an OR of 26% was reported for carboplatin in non-refractory patients [18], and ORs of 27–59% were reported for cisplatin and carboplatin in patients with platinum-free intervals of between 5 and 24 months [8,9].

The activity of ZD0473 against platinum-resistant disease indicates that it does not offer a marked therapeutic advantage compared with conventional platinum-based agents, with OR rates of 8.3% for ZD0473, 4% for carboplatin [18], and 17% for cisplatin [8]. It therefore appears that ZD0473 may not completely circumvent the platinum-resistance mechanisms present in platinum-resistant disease. This observation may also be appropriate for other platinum-based agents, as indicated by the finding that oxaliplatin produces an OR rate of 16% against platinum-pretreated advanced disease [19]. BBR 3464, a novel trinuclear platinum agent, has shown differential preclinical activity in ovarian cancer cell lines compared with cisplatin [20] in a similar manner to ZD0473. In phase I clinical trials in patients with ovarian cancer, BBR 3464 has proven to have good tolerability, but its efficacy is yet to be evaluated [21].

As an alternative to platinum-based agents, a number of non-platinum agents have been examined against platinum-resistant disease, and some preliminary studies have suggested evidence of promising efficacy. Etoposide has been shown to produce an OR rate of 27% in platinum-resistant disease [22], vinorelbine an OR rate of 21% [23] and dose-intense paclitaxel an OR rate of 48% in platinum-resistant, recurrent disease [24]. However, the use of these agents can be troubled by tolerability issues, as reflected by the need for stem cell support with dose-intense paclitaxel [24] and dose-limiting haematological toxicity with etoposide [22]. Overall, the activity of ZD0473 in relapsed disease is similar to the cumulative data on many of the newer agents [7].

The TTP and TTD data reported in this study demonstrate that the sensitive patients respond to ZD0473 with longer median TTP and TTD than the platinum-resistant patients. The median TTP and TTD values for the platinum-sensitive patients are better than those reported for oxaliplatin and paclitaxel in platinum-pretreated advanced disease [19]. However, longer median TTP and TTD values in both platinum-sensitive and -resistant sub-groups than the values reported in this study have been reported for agents such as etoposide [22]. Overall, a similar pattern is reported in many studies to that reported here, whereby the platinum-sensitive patients exhibit longer TTD and TTP periods than the platinum-resistant patients [8,19,22].

In conclusion, this study indicates that ZD0473 is well tolerated in the second-line treatment of advanced ovarian cancer. Beneficial efficacy is particularly apparent in platinum-sensitive disease, where it offers approximately equivalent activity to currently approved agents. Resistance mechanisms appear to remain in resistant disease such that ZD0473 monotherapy is not associated with markedly better responses than cisplatin in this patient group. It remains to be seen whether ZD0473 in combination with liposomal doxorubicin [25] or paclitaxel [26] offers any therapeutic advantages over current combinations of cisplatin or carboplatin.

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