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Phase II trial of ZD0473 as second-line therapy in mesothelioma

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Abstract

A phase II, open-label, non-comparative, multicentre trial of the platinum analogue ZD0473 as second-line therapy for pleural mesothelioma has been completed. The objectives were to evaluate the activity and tolerability of ZD0473 in patients with relapsed or progressive disease who had received one prior chemotherapy regimen. Forty-seven patients were recruited onto the trial, all aged >18 years with a life-expectancy >12 weeks, and World Health Organization (WHO) performance status ≤2. A starting dose of 120 mg/m^2 was administered to 14 patients, six of whom subsequently had their dose escalated to 150 mg/m^2. Thirty-three patients received a starting dose of 150 mg/m^2. In total, 147 treatment cycles were administered (median number of cycles 3 [range 1–6]). The main toxicity of ZD0473 was haematological (thrombocytopenia) and the most common non-haematological adverse event was nausea. There was no clinically significant nephro-, neuro-, or oto-toxicity. Of the 43 patients evaluable for response, 12% had a minor response (defined by a reduction in lesion size ≥10% but <50%), 44% had stable disease, 40% had disease progression, and two patients died before an objective response could be assigned. Median time to progression and death in evaluable patients was 77 days (95% confidence interval [CI]: 44, 105 days) and 203 days (95% CI: 165, 277 days), respectively. In conclusion, although ZD0473 demonstrated a manageable tolerability profile, no complete or partial responses were seen in second-line treatment of mesothelioma. This trial also demonstrates that clinical trials in second-line mesothelioma patients are feasible.

Keywords: Mesothelioma; Chemotherapy; ZD0473; Second-line

1. Introduction

1.1. Mesothelioma: incidence and survival

Asbestos exposure remains the principal cause of pleural mesothelioma. The incidence has risen steadily since the disease was first described in 1931, and 3000 new cases are diagnosed each year in the USA [1]. Since there is generally a 30–40 year latent period [2] between exposure and the development of clinical symptoms, incidence is expected to continue to rise over the next decade and reach 1500 deaths per year in Britain by 2010 [3].

The prognosis for patients with mesothelioma depends on the stage of disease at diagnosis. Most patients are not diagnosed until the disease is at a more advanced stage, when median survival is approximately 9 months from the time of diagnosis [4]. There are a few reports of a small series of patients with mesothelioma that has not metastasised to the lymph nodes, who have been treated with combined modality treatment and have shown 5-year survival as high as 39% [5].

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1.2. Clinical trials in malignant mesothelioma

Unfortunately, clinical trials in pleural mesothelioma are scarce compared with clinical trials for other tumours [6]. There is no standard first-line therapy for mesothelioma patients [6], although several treatment options are available, including surgery, radiotherapy and chemotherapy. Local therapy is limited to patients who have relatively small volume disease without mediastinal lymph node involvement. Surgical therapy in patients with limited-disease pleural mesothelioma remains experimental and may correlate with a high post-operative mortality rate.

1.3. Treatment of mesothelioma

Surgical procedures for malignant pleural mesothelioma include: thoracoscopy with sclerosis, palliative treatment, and treatment with curative intent, such as pleurectomy/decortication. Patients with resectable tumours can be offered extrapleural pneumonectomy, but this is an aggressive procedure which may lead to complications such as respiratory failure, pneumonia or bronchial air-leaks [6]. Improvements in survival may be achieved through the use of multimodal therapy, which usually involves surgery with adjunct radiotherapy, chemotherapy or both [1]. Radiotherapy is complicated by the large radiation field and high doses required to treat the entire pleura which must not exceed the maximum recommended dose for the surrounding organs such as the heart, lung, liver, spinal cord and oesophagus [7].

A major complication associated with chemotherapy treatment for mesothelioma is resistance to chemotherapeutic agents. Mesothelioma is associated with both glutathione-S-transferase- and P-glycoprotein-mediated resistance mechanisms [8], which may be inherent or acquired and often lead to the failure of treatment regimens.

1.4. Chemotherapy regimens for mesothelioma

There have been few systematic clinical trials where single-agent or combination chemotherapy have been used in the treatment of mesothelioma [9], and of the agents tested, many have had little or no success, such as plant alkaloids [7] and gemcitabine [10]. Until recently, the most successful single-agents have included ifosfamide, vinorelbine and methotrexate, which have demonstrated overall response rates of 24% [11], 24% [12], and 37% [13], respectively. However, the median survivals for these regimens from the time of diagnosis was low (9, 13.8 and 11 months, respectively). Cisplatin and doxorubicin have also been used as single-agent therapies, and produced response rates of 14% and 11%, respectively, in combined analyses [14]. One trial has shown a response rate of 36% with high-dose cisplatin and survival of 2–8 months [15]. In addition, palliative mitomycin-C, vinblastine and cisplatin treatment has been shown to provide symptomatic benefits to patients with advanced, inoperable malignant mesothelioma [16]. From these results, it appears that the successful treatment of mesothelioma awaits the discovery of active drugs.

ZD0473 is a new platinum agent designed to overcome resistance mechanisms [17], such as those seen in mesothelioma [8]. Treatment of second-line patients has not been considered important or effective in the past, as it was thought that clinical trials in such patients could not be established due to low patient numbers and short survival periods. As a result, no clinical trials have focused solely on this patient population until now. This paper presents data from the first chemotherapy clinical trial evaluating the efficacy and tolerability of ZD0473 in second-line patients with advanced mesothelioma.

The primary objective of the trial was to measure the objective tumour response rate of ZD0473 in patients with second-line mesothelioma who had failed one prior chemotherapy regimen. Secondary objectives included assessment of the safety, tolerability and clinical benefit (relief of disease-related symptoms) of ZD0473.

2. Methods

This was a phase II, open-label, non-comparative, multicentre trial.

2.1. Patients

Patients eligible for this trial had histologically confirmed malignant pleural mesothelioma, with any tumour extension (according to International Mesothelioma Interest Group [IMG] Tumour-Node-Metastasis criteria [TNM]) and at least one target lesion as defined by the National Cancer Institute (NCI) Response Evaluation Criteria in Solid Tumours (RECIST). Tumour thickening was >2 cm and measurable on at least two contiguous sections of a computer tomography (CT) scan. Patients included in the trial: had relapsed or progressive disease after receiving one prior chemotherapy regimen, were aged >18 years with a life expectancy >12 weeks, and had a World Health Organization (WHO) performance status of ≤ 2. Patients receiving palliative radiation therapy for painful lesions or prevention of metastases along biopsy tracks were allowed to enter the trial. Written, informed consent was obtained from each patient.

Patients excluded from the trial had received prior intracavitary drugs other than talc, tetracycline or atabrine, undergone any prior systemic anti-cancer therapy ≤ 2 weeks prior to the start of the trial, and had unresolved toxicity from prior anti-cancer treatment (other than non-haematological toxicity $\leq$grade 2). Patients receiving prior radiation therapy to only one target lesion were excluded unless the lesions were clearly progressive and the interval between radiotherapy and registration onto the trial was ≥ 4 weeks.

2.2. Treatment

Patients received a starting dose of 120 mg/m^2 ZD0473 by intravenous infusion on Day 1 of a 3-week cycle. The dose was escalated to 150 mg/m^2 provided the starting dose was well tolerated. Following a safety review, the starting dose was modified to 150 mg/m^2.

A dose delay of ≥3 weeks was permitted between consecutive treatments. Patients had to meet the following criteria before the start of each cycle: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and serum creatinine concentration or bilirubin concentration ≤1.25 × the upper limit of the normal range. If the criteria were not met by Day 28, the dose was reduced for the next cycle. If criteria were not met by Day 42, the patient was withdrawn from the trial. Patients showing no disease progression continued treatment for six cycles or until the withdrawal criteria were met. If the investigator considered it to be in the best interest of the patient, therapy could be continued beyond six cycles.

No other systemic anti-cancer therapies were permitted. The prophylactic use of anti-emetics (serotonin antagonists) was recommended during all cycles and patients were allowed supportive care measures and symptomatic treatment for any drug-related toxicity.

2.3. Tolerability assessments

Tolerability was assessed using the NCI-Common Toxicity Criteria (NCI-CTC) grading system. Patients underwent routine physical examinations at the beginning of each cycle, and laboratory assessments (blood chemistries and haematology) were performed weekly. Urinalysis assessments were performed at the start of each cycle, if clinically indicated.

2.4. Efficacy assessments

Baseline objective tumour assessments were performed ≤4 weeks prior to the start of trial therapy and ≥3 weeks after any previous anti-cancer therapy. Objective tumour response was assessed by measurement of tumour target lesions using the revised WHO-RECIST guidelines. Clinical benefit, as measured by disease-related symptom relief (quality of life), was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the lung cancer subscale (LCS).

3. Results

3.1. Patients

Forty-seven patients with pleural, second-line mesothelioma were recruited onto the trial. The majority of patients (80%) had advanced disease (stage II–IV), and 83% had received prior platinum therapy. Patient demography is shown in Table 1.

Table 1
Patient demography

	No. patients ($n = 47$)
Median age, range (years)	59 (37–75)
Gender	
male	41
female	6
WHO performance status	
0	4
1	32
2	11
Stage of disease[a]	
IA	4
IB	5
II	5
III	13
IV	19
Prior therapy	
surgery	19
chemotherapy	47
platinum therapy	39
immunotherapy/hormonal therapy	2
radiotherapy	19
other	1
Platinum-free interval (months)	
0–3	19
4–6	7
7–12	9
13–24	3
≥ 25	1
Creatinine clearance (ml/min)	
< 60	2
60–79	10
≥ 80	35

[a]Data not available for 1 patient. WHO, World Health Organization.

3.2. Treatment

Fourteen patients received a starting dose of 120 mg/m^2 (Group 1), six of whom subsequently had their dose escalated to 150 mg/m^2 (Group 2). Thirty-three patients received a starting dose of 150 mg/m^2 (Group 3). A total of 147 treatment cycles were administered, and overall, patients received a median number of 3 cycles (range 1–6), with 13% receiving ≥6 cycles (Table 2). Details of dose reductions and dose delays are also shown in Table 2. There were dose delays of >7 days, but no longer than 14 days, in 4 patients.

3.3. Tolerability

The main toxicity of ZD0473 was haematological, with thrombocytopenia occurring most frequently (Table 3). Nausea was the most common non-haematological adverse event at all grades (Table 4), while dyspnoea was the most common non-haematological toxicity at ≥grade 3 (27.7%

Table 2
ZD0473 treatment cycles and dose delays per dose group

	Group			
	1 ($n = 8$)	2 ($n = 6$)	3 ($n = 33$)	overall ($n = 47$)
Total no. cycles	27	27	93	147
Median no. cycles (range)	3.4 (2–6)	4.5 (3–6)	2.0 (1–6)	3.0 (1–6)
Patients without dose delay or reductions, *n*	6	6	27	39
Patients with cycles delayed, *n*	6	3	10	19
Patients with cycles delayed due to toxicity, *n*	4	2	6	12
Patients receiving ≥6 cycles, *n*	2	2	2	6
Patients with dosage reduced ≥20%, *n*	1	0	5	6

of patients). No patients experienced clinically significant nephro-, neuro-, or oto-toxicity.

All patients eventually withdrew from the trial: five patients withdrew due to adverse events (treatment-related in three patients), and a further 29 patients withdrew due to disease progression. Patients were followed-up after discontinuation of trial therapy and by the time of data cut-off, 35 patients had died.

3.4. Efficacy

Forty-three patients were evaluable for tumour response. No complete or partial responses were seen, but five patients had a minor response (as defined by a reduction in lesion size of ≥10%, but not great enough to be classified as a complete or partial response), 19 patients had stable disease, and 17 patients had disease progression (Fig. 1). A further two patients died before an objective response could be assigned. Disease control rate (minor response and stable disease for at least 6 weeks) was 55.8% (95% confidence interval [CI]: 39.9%, 70.9%), and median time to progression and death in the evaluable patients were 77 days (95% CI: 44, 105 days) and 203 days (95% CI: 165, 277 days), respectively.

Forty patients completed the FACT-L questionnaire. There was little change in patients' quality of life throughout the trial, and the median score for the LCS and the overall FACT-L questionnaire did not alter significantly.

Table 3
No. patients (%) experiencing grade 3/4 haematological toxicity, worst grade per patient

	Group			
	1 ($n = 8$)	2 ($n = 6$)	3 ($n = 33$)	overall ($n = 47$)
Anaemia	1 (12.5)	0	3 (9.1)	4 (8.5)
Leucopenia	1 (12.5)	2 (33.3)	7 (21.2)	10 (21.2)
Neutropenia	1 (12.5)	2 (33.3)	6 (18.2)	9 (19.1)
Thrombocytopenia	3 (37.5)	2 (33.3)	12 (36.4)	17 (36.2)

Table 4
No. patients (%) per group with non-haematological toxicities[a], irrespective of causality, all grades

	ZD0473 dose (mg/m^2)			
	1 ($n = 8$)	2 ($n = 6$)	3 ($n = 33$)	overall ($n = 47$)
Anorexia	0	1 (16.7)	10 (30.3)	11 (23.4)
Chest pain	2 (25.0)	0	10 (30.3)	12 (25.5)
Constipation	3 (37.5)	2 (33.3)	15 (45.5)	20 (42.6)
Dyspnoea	6 (75.0)	1 (16.7)	13 (39.4)	20 (42.6)
Malaise	5 (62.5)	2 (33.3)	13 (39.4)	20 (42.6)
Nausea	7 (87.5)	2 (33.3)	19 (57.6)	28 (59.6)
Pain	3 (37.5)	2 (33.3)	5 (15.2)	10 (21.3)
Vomiting	3 (37.5)	0	8 (24.2)	11 (23.4)

[a]Occurring in ≥15% of the patient population.

4. Discussion

This trial is the first to demonstrate that clinical trials in patients with pleural mesothelioma are feasible in second-line, and it paves the way for further clinical trials with the aim of establishing an appropriate therapy for second-line mesothelioma. Second-line agents must alleviate symptoms and cause minimal side effects, resulting in an improved quality of life for the patient. ZD0473 demonstrated a manageable tolerability in mesothelioma

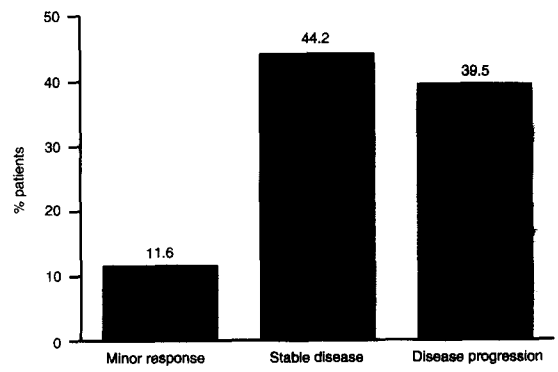

Fig. 1. Tumour response to ZD0473 treatment. 43 patients evaluable; 2 patients died.

patients treated in second-line trials, and as seen in other phase II trials in patients with solid malignancies, no patients suffered from clinically significant nephro-, neuro- or oto-toxicity [18,19].

Survival in second-line patients receiving ZD0473 (just under 7 months) is comparable to survival in first-line patients receiving cisplatin (2–8 months) [15]. This suggests that selected patients may be candidates for second-line therapies which may further improve survival for patients with mesothelioma. Since a relatively high number of patients experienced stable disease or minor response following ZD0473 treatment, ZD0473 may prove to be a useful agent for combination regimens. Currently, the most common treatments for first-line mesothelioma involve cisplatin in combination with agents such as doxorubicin, mitomycin or doxorubicin-ifosfamide. These combinations have resulted in response rates of 18–25% in malignant pleural mesothelioma and have been extensively used in recent years [16,20,21]. In a recently reported phase III study, combination treatment with cisplatin and the antifolate, pemetrexed, resulted in a response rate of 41% in chemonaive patients with malignant pleural mesothelioma compared with 17% of patients who were randomised to treatment with cisplatin alone [22]. Furthermore, patients who received the combination treatment had a median survival of 12.1 months compared with 9.3 months for those who received cisplatin alone ($P = 0.02$). Patients receiving pemetrexed plus cisplatin received folic acid and vitamin B_{12} supplements to reduce the incidence of drug-related deaths associated with febrile neutropenia and diarrhoea; however, 14% of patients still experienced grade 3/4 neutropenia.

ZD0473 has an improved tolerability profile in comparison to cisplatin and may therefore offer a viable alternative in combination regimens. Despite the lack of efficacy of the single-agent gemcitabine [10], the combination of cisplatin and gemcitabine in first-line mesothelioma produced an objective response rate of 47.6%, with a median survival of 41 weeks and significant clinical benefit in the improvement of symptoms [23]. Oxaliplatin has also demonstrated some success in the treatment of mesothelioma when used in combination with other agents [24,25]. Therefore, it is possible that ZD0473 may have a future as a combination agent, despite showing little activity as a second-line single agent in mesothelioma patients.

5. Conclusions

This trial is the first to demonstrate that phase II trials in second-line mesothelioma patients are possible. Future trials in second-line patients must focus not only on the activity of agents, but also on improvements in survival time and quality of life.

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