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Short communication

A phase II study of the platinum analogues JM8 and JM9 in malignant pleural mesothelioma

Brian M. J. Cantwell[1], C. R. Franks[2] and Adrian L. Harris[1]

[1] University Department of Clinical Oncology, Regional Radiotherapy Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, England
[2] Pharmaceutical Research and Development Division, Bristol Myers International Corporation, Brussels

Summary. The platinum analogues JM8 and JM9 were assigned randomly to 16 patients with pleural mesothelioma. Nine patients received JM8 and seven received JM9. Two of nine (22%) JM8-treated patients had objective responses (confidence limits 2.8%–60.0%, 95% confidence level). JM9 was more emetogenic than JM8, but not to a significant level. However, patients who received JM9 significantly preferred this drug to be given on an inpatient basis, in contrast with patients receiving JM8, who received the majority of courses as outpatients.

Primary cytotoxic drug resistance is a major obstacle to successful treatment of mesothelioma, and phase II studies of novel agents should continue in an effort to circumvent this problem.

Introduction

Malignant mesothelioma is poorly responsive to established cytotoxic chemotherapy. No responses occurred in 30 patients treated in a randomised trial of doxorubicin versus cyclophosphamide [9]. The Eastern Cooperative Oncology Group found that seven of 51 patients had responses with doxorubicin; two of 24 patients responded to doxorubicin in combination with other cytotoxic drugs, and when doxorubicin was given to patients with previous chemotherapy a single response occurred in 28 patients [6]. It was similarly found that doxorubicin had little activity as a second-line agent in a study that demonstrated the ineffectiveness of single-agent 5-fluorouracil as first chemotherapy for malignant mesothelioma [4]. It is clear that phase II trials of novel agents should be performed on patients with mesothelioma in an effort to identify better therapies. A phase II study of *m*-AMSA found this drug to have little activity in malignant mesothelioma [3]. Conventional antifolates such as methotrexate have shown no activity in mesothelioma, but have been studied in too few patients [1]. A phase II study of the novel antifolate N^{10}-propargyl-5, 8 dideazafolic acid (CB3717) in 18 patients with mesothelioma showed poor antitumour activity and induced frequent but reversible hepatic toxicity with associated malaise [2].

Offprint requests to: B. M. J. Cantwell

Cisplatin combined with doxorubicin produced four objective responses in six patients with mesothelioma [11]. A phase II trial of high-dose cisplatin (120 mg/m^2) showed modest antitumour activity (11% response rate; 95% confidence limits 2%–32%) in 18 patients with mesothelioma [8]. The major clinical disadvantages of cisplatin include its emetogenic effect and the possibility of renal impairment which can be life-threatening and may be at least partially irreversible [5]. In an attempt to maintain or increase antitumour activity but decrease toxicity, the platinum analogues JM8 (CBDCA, carboplatin) and JM9 (CHIP) have been developed [5].

Patients and methods

As part of a randomised, broad phase II multicentre trial, we studied the effects of either JM8 or JM9 in 16 patients with histologically proven pleural mesothelioma. All 16 patients had assessable disease which was progressive at the start of platinum analogue therapy, despite prior therapies in some patients. Patient characteristics are given in Table 1. Patients' performance status and toxicities were graded by World Health Organisation (WHO) criteria [10]. Each platinum analogue was administered once monthly as a 30-min intravenous infusion. Before treatment and weekly during treatment full blood counts were made and hepatic and renal biochemical parameters were recorded. Doses were 400 mg/m^2 for JM8 and 300 mg/m^2 for JM9 and modifications were made for myelotoxicity (Table 2). Treatments were given if possible in the outpatient clinic, but some courses were given in hospital at patients' specific request. Response was assessed by serial chest X-ray (CXR) and computerised tomographic (CT) scans of chest. Routine antiemetics were given with each course, usually oral dexamethasone 4 mg q. d. s. for 1 day and oral domperidone 30 mg q. d. s. for 2 days or longer.

Results

Two of nine (22%) JM8-treated patients had >50% decrease of tumour volume on serial CXR and CT scans. The confidence limits for this response rate were 2.8%–60.0%, 95% confidence level. Neither patient had had prior radiotherapy, but one had had an objective response to previous CB3717 of 7 months duration before relapse occurred and JM8 was initiated. The duration of JM8-induced response was 5 and 6 months respectively, and each patient had a

Table 1. Patient characteristics in nine JM8-treated and seven JM9-treated cases of malignant pleural mesothelioma

	JM8	JM9
Median age (range) in years	58 (41–74)	58 (45–63)
Median performance status (range)	2 (1–3)	2 (1–3)
	Number of patients	
	JM8	JM9
Extent of disease		
Localised to one hemithorax	6	6
Extrathoracic spread	3	1
Previous treatments		
Incomplete debulking surgery	2	3
Radiotherapy[a]	1	1
Chemotherapy[b]	3	3
History of asbestos exposure	6	7

[a] Intrapleural radioactive colloidal yttrium after incomplete debulking surgery

[b] CB3717 in five cases, combined ifosfamide and doxorubicin in one case

Table 2. Courses and doses of the platinum analogues JM8 and JM9

	JM8	JM9
Total number of courses	32	16
Median (range)	3 (1–6)	2 (1–4)
Monthly dose	400 mg/m^2	300 mg/m^2

Two patients >70 years old started JM8 at 360 mg/m^2 and 300 mg/m^2 respectively; the latter subsequently had dose escalations. One course of JM8 and one course of JM9 were given at reduced dose because of myelosuppression. Two patients receiving JM8 and one receiving JM9 had dose escalations to 110% of starting doses on some courses

Table 3. Toxicity according to WHO grading

	JM8 (32 courses in nine patients)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Serum creatinine	32	0	0	0	0
Haemoglobin	21	10	1	0	0
WCC	19	10	3	0	0
Platelets	32	0	0	0	0
Nausea/vomiting[a]	1	2	24	5	0
	JM9 (16 courses in seven patients)				
Serum creatinine	16	0	0	0	0
Haemoglobin	12	2	1	1	0
WCC	15	1	0	0	0
Platelets	14	0	2	0	0
Nausea/vomiting[b]	0	0	11	5	0

[a] The highest WHO grade of nausea/vomiting per course was recorded despite pretreatment with anti-emetics

[b] Severe nausea/vomiting requiring modification of anti-emetic therapy (grade 3 WHO) was more frequent during JM9 compared with JM8 treatment, but this effect was not significant (5/16 vs 5/32: $\chi^2 = 0{,}4$, df = 1, $P < 0.52$)

total of six JM8 courses. Two JM8-treated patients had static disease for 4 and 6 months, and in five patients the disease progressed despite JM8. None of seven JM9 patients responded, and confidence limits for this observation were 0.0%–49.9%, 95% confidence level.

Toxicity

One JM8-treated patient had only one course of treatment, refusing further treatment because of JM8-associated nausea and vomiting. This patient had also had difficulty in tolerating prior chemotherapy (doxorubicin/ifosfamide). Two JM9-treated patients each received only one course. In one case the disease progressed rapidly and the patient died 4 weeks after the first treatment. The other patient, who had only one functional eye following old trauma, developed episodic scintillating scotomata lasting a few minutes, and these re-occurred about once a week for 8 weeks. This patient had pre-existing ischaemic heart disease and was taking anti-platelet drugs, but JM9-induced ocular toxicity could not be excluded. Details of toxicity according to WHO grading are given in Table 3. Additionally, one JM8-treated patient developed facial flushing and another JM8-treated patient developed transient dizziness after JM8 infusions, but treatment cycles were not altered because of these effects. Two JM9-treated patients had mild transitory diarrhoea after some courses, and one patient developed a red macular rash. These effects per se did not lead to alteration of JM9 therapy. Twenty of 32 JM8 courses (62.5%) were given on an outpatient basis and the remaining 12 were given to inpatients. In contrast only two of 16 JM9 courses (12.5%) were given in the outpatient clinic, 14 on an inpatient basis. Thus it was possible to give significantly more outpatient JM8 than JM9 courses ($\chi^2 = 10.3$, $df = 1$, $P < 0.005$).

Discussion

JM8 appears to have modest anti-tumour activity in malignant mesothelioma, with no clinically significant nephrotoxicity and mild manageable myelosuppression. Mbidde et al. (1986) recorded two objective responses (one CR, one PR) in 17 patients with malignant mesothelioma in a phase II study [7]. Responses were apparent after two courses, and our findings with JM8 are similar. More than 50% of our JM8 courses could easily be administered in the outpatient clinic, and in the patients who responded, response was apparent with associated symptom relief after three courses.

The apparent lack of response in seven JM9-treated patients does not preclude JM9 as a potentially active drug in mesothelioma, as the numbers studied are small. JM9, however, was less easy to use clinically on an outpatient basis in mesothelioma patients and resulted in a greater hospitalisation rate than JM8. Further study of the platinum analogues in mesothelioma continues. JM8 might be combined with doxorubicin, the single most active established agent [1] in future studies in mesothelioma. This combination is likely to have significant myelosuppressive potential. Primary cytotoxic drug resistance is a major obstacle to successful treatment of mesothelioma, and therefore phase II studies of novel agents as primary treatment should also continue.

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