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Clinical trial report

Phase II study of fotemustine in untreated inoperable non-small-cell lung cancer

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Abstract. A total of 43 patients with advanced, previously untreated non-small-cell lung cancer (NSCLC) were treated with a novel nitrosourea, fotemustine, given at 100 mg/m^2 on days 1 and 8. Maintenance treatment consisted of a single injection of 100 mg/m^2 given every 21 days. 37 patients were evaluable for respone. Of these, 5 patients had a partial response (13.5%; 95% confidence interval, 6%–28%). Toxicity comprised mainly anaemia and thrombocytopenia. Other toxicities were mild. This phase II study confirms that fotemustine is a moderately active and well-tolerated drug in NSCLC.

Key words: Lung cancer – Chemotherapy – Fotemustine – Phase II

Introduction

Fotemustine is a nitrosourea containing an α-aminophosphonic acid group. It was synthesised with the intention of creating a molecule that would be better capable of crossing the blood-brain barrier and have enhanced activity.

Following phase I studies [1], Le Chevalier et al. [5] reported a 12.5% response rate [95% confidence interval (CI), 2%–22%] in 40 patients with squamous-cell carcinoma of the lung, 43% of whom had had prior chemotherapy. This is an encouraging result in view of the low response rates obtained using other agents in the treatment of patients with squamous carcinoma of the lung, especially those who have previously been treated. The present study was therefore undertaken to determine the activity of fotemustine in previously untreated patients with non-small-cell lung cancer (NSCLC).

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Patients and methods

Patients were eligible if they had measurable or evaluable disease and had not previously been treated with chemotherapy. Patients could have received prior radiotherapy, provided that they had completed it 28 days before starting fotemustine therapy. Patients with untreated asymptomatic brain metastases were eligible. Entry criteria included an age of ≤75 years, a Karnofsky score of ≥60%, a life expectancy of >3 months, a haemoglobin value of ≥100 g/l, a neutrophil count of ≥2×10^9/l and a platelet count of 100×10^9/l; in addition serum levels of transaminases, alkaline phosphatase, bilirubin and γ-glutamyl transpeptidase (γGT) needed to be ≤2.5 times the upper normal limit and creatinine and urea values, ≤1.5 times the upper limit of normal. Patients were excluded if they had had a previous malignancy (other than completely removed basal-cell skin carcinoma or in situ cervical cancer), uncontrolled infection or heart failure, if there existed a foreseeable difficulty in treatment or follow-up or if they were receiving other cytotoxic drugs. All patients gave written informed consent. The study was approved by the ethical committees of the participating hospitals.

The treatment was carried out in two phases: an induction cycle, received by all patients, and 3-weekly maintenance cycles, which were given to patients who had achieved a response or had stable disease. During the induction cycle, 100 mg/m^2 of fotemustine was given on days 1 and 8 in 250 ml of glucose. The infusion solution was protected from light and the procedure lasted no longer than 1 h. No pre- or post-treatment hydration was carried out; anti-emetic therapy was given according to local practice. Dose modifications were made on the basis of liver-function tests and neutrophil and platelet counts. The dose was reduced to 75% if the neutrophil count was 1,500–1,999/l or the platelet count was 80,000–100,000/l. The dose was reduced to 50% if neutrophils numbered 1,000–1,499/l. If the neutrophil count was <1,000/l or the platelet count was <80,000/l the treatment was delayed. During the induction cycle, toxicity was assessed on days 22, 36 and 43 for toxicity, disease state and quality of life using the Spitzer Quality-of-Life Index as completed by the doctor, nurse or trial co-ordinator.

Maintenance treatment consisted of a single 100-mg/m^2 injection of fotemustine given every 3 weeks, when response, toxicity and quality of life were recorded. Patients remained on treatment until there was objective evidence of disease progression or severe toxicity.

Response was assessed on day 43. WHO criteria were used. A complete response (CR) was defined as the disappearance of all signs of disease both clinically and on chest X-ray or hepatic ultrasound. A partial response (PR) was defined as a 50% decrease in the sum of perpendicular diameters of all measurable lesions. A minor response represented a 25%–50% decrease in the sum of

perpendicular diameters of all measurable lesions. Stable disease (SD) meant either no change or a response less than a minor response. Progressive disease (PD) was defined as an increase of >25% in the sum of perpendicular diameters of any lesion. All responses had to be maintained for at least 4 weeks.

Results

From June 1991 to April 1992, 43 eligible patients were recruited into the study. The characteristics of the patients on admission to the study are listed in Table 1. In all 16 patients had locally advanced disease, 17 had metastases at 1 site only, and 10 had metastases at ⩾2 sites. Sites of metastases were as follows: lymph nodes, 16; bone, 14; lung, 4; brain, 2; liver, 3; skin, 1; and bone marrow, 1. Histology was squamous in 16 cases, adenocarcinoma in 11, large-cell undifferentiated in 9 and undifferentiated non-small-cell in 7. Overall 67% of the patients (29) had local or distant metastases on admission to the study and 72% (31) had a Karnofsky score of between 60% and 80%. None of the patients had previously received chemotherapy, but 3 had had lung radiotherapy; 3, laser therapy; and 5, surgery.

Response

The response rates are presented in Table 2. Of 43 patients, 37 were evaluable for response assessment. Altogether, 5 patients achieved a PR (13.5%; 95% CI, 6%–28%). Another 12 patients had SD. In all, 6 patients were considered non-evaluable for response. The reasons were: 1 patient died of cardiac arrest (day 27), 1 died at day 9, 1 proved to have unassessable disease on review, 1 was lost to follow-up, 1 had cardiac failure and 1 had SD at day 36 and was then given alternative chemotherapy. The median time to response was 6 weeks (range, 6–18 weeks). The median response duration was 25 weeks, the range being 6–32 weeks (6, 16, 25, 27 and 32 weeks, respectively) and the mean, 21 weeks. A total of 19 patients received maintenance chemotherapy (median number of cycles received, 2; range, 1–8).

Toxicity

Toxicity data are presented separately for the induction cycle and the maintenance cycles in Table 3.

Induction cycle. A total of 43 patients were evaluable for toxicity during the induction cycle, including the patient with mesothelioma. One patient died on day 9. There was no treatment delay in the induction cycle. The commonest toxicity was anaemia of WHO grades 1–4, experienced by 51% of the patients. Grades 3 and 4 anaemia, neutropenia and thrombocytopenia were experienced by 7%, 2% and 12% of the patients, respectively, and 3 patients required platelet transfusion. Transient liver-enzyme elevations of grade 2 and above were noted for alkaline phosphatase, aspartate aminotransferase (AST) and γGT in 8%, 13% and

Table 1. Patients' characteristics

Number	43
Sex (M/F)	26/17
Mean age (range)	63 (47–75) years
Mean Karnofsky score, % (range)	78 (60–100)
Karnofsky scores, %:	
100	3
90	9
80	12
70	13
60	6
Histology:	
Squamous	16
Adenocarcinoma	11
Large-cell undifferentiated	9
Undifferentiated	7
Disease assessment:	
Measurable	13
Evaluable	21
Both	9

Table 2. Responses to induction and maintenance cycles of fotemustine, corresponding to the maximal responses in either the induction or the maintenance cycles

Response	Number (%)		95% CI
Total	37		
PR	5	(13.5)	6%–28%
SD	12	(32.4)	
PD chest	12		
PD metastases	5		
PD chest, metastases	3		
Non-evaluable	6		

Table 3. Worst toxicity recorded for each patient, expressed as a percentage of the total population

Toxicity		WHO grade				
		0	1	2	3	4
Haematological:						
Anaemia	(I)	51	28	14	5	2
	(M)	50	33	17	0	0
Neutropenia	(I)	74	12	12	2	0
	(M)	78	22	0	0	0
Thrombocytopenia	(I)	67	5	16	7	5
	(M)	77	6	0	11	0
Liver-function tests:						
Alk. Phos.		62	30	8	2	2
AST/SGOT		79	10	5	3	3
γGT		61	13	16	5	5
Bilirubin		92	8	0	0	0
Nausea and vomiting[a]	(I)	70	14	11	5	0
	(M)	53	22	22	5	0
Infection	(I)	91	0	7	2	0
	(M)	90	0	5	5	0

I, Induction therapy; M, maintenance treatment; Alk. Phos., alkaline phosphatase. There was no case of grade 3 or 4 elevation of liver-enzyme values

[a] These data refer to the number of occurrences per administration rather than to the worst episode of nausea/vomiting per patient

26% of the patients, respectively. In the table, nausea and vomiting in the induction cycle is reported per administration (i.e., two WHO scores) rather than as a global score per patient. On 30% of administrations, patients reported nausea and vomiting, with 16% corresponding to grades 2 and 3; no patient experienced grade 4 symptoms.

Maintenance cycles. A total of 19 patients had maintenance cycles. In all, 2 patients had treatment delays, both for thrombocytopenia (7 and 5 days, respectively), and 3 patients had dose reductions for neutropenia or thrombocytopenia.

Quality of life

Quality of life was assessed each time a patient was seen at one of the participating hospitals. The Spitzer Quality-of-Life Index was used. Before treatment the mean score was 7.3 ($\pm$032), and at the end of the induction cycle the mean score was 7.2 ($\pm$0.42).

Discussion

Fotemustine has been shown to have activity in NSCLC [5] and in malignant melanoma [2, 3], where an overall response rate of 24% has been obtained, including a 25% response rate in patients with cerebral metastases. These are encouraging results in these chemotherapy-resistant tumours. Clinical tolerance of the drug has been reported to be good, with myelosuppression being the major dose-limiting toxicity.

There are few cytotoxic drugs that show activity in NSCLC. In a review of 134 phase II studies in NSCLC, Kris et al. [4] indicated that other nitrosoureas [carmustine (BCNU), lomustine (CCNU), methyl-CCNU] were associated with a response rate of $<15\%$, and only 6 agents had a response rate of $>15\%$. The response rate of 12.5% reported by Le Chevalier et al. [5] is therefore of especial interest since 17 of the 40 patients had received previous chemotherapy. The 13.5% response rate reported herein in untreated patients is disappointing in comparison with that reported by Le Chevalier et al. However, the drug is undoubtedly active, although its superiority to other nitrosoureas cannot be judged from the reported results. The toxicity profile is as previously reported, consisting mainly of myelosuppression with little nausea and vomiting and mild elevation of hepatic enzymes. Fotemustine can be given on an out-patient basis. This pattern of toxicity makes the combination of fotemustine with non-myelosuppressive agents worthy of further study.

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