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Original Paper

A Phase II Trial of Fotemustine and Cisplatin in Central Nervous System Metastases From Non-small Cell Lung Cancer

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A phase II study was conducted in order to determine the feasibility and toxicity of cisplatin combined with the nitrosourea fotemustine in central nervous system metastases from non-small cell lung cancer. 31 chemotherapy-naïve patients were included between November 1990 and April 1993. Computed tomography scan-documented tumour regression in brain metastases was observed in 7 of the 25 evaluable patients, but only 4 of these (16%) lasted more than 4 weeks. In 2 of these 4 patients, the response on central nervous system metastases was considered as complete. The median duration of response was 20.5 weeks and the median survival was 16 weeks overall and 28.5 weeks for responding patients. The limiting toxicity of this regimen was haematological. 2 patients died from infectious pneumonitis while in neutropenia. Treatment delays due to haematological toxicity occurred in 57% of patients. Despite the rather encouraging response rate, such toxicity appears too high when compared to the overall bad prognosis of this population of patients. Cranial radiotherapy remains the standard treatment in this setting and should only be compared in the future to less aggressive schedules.

Key words: non-small cell lung cancer, central nervous system metastases, chemotherapy, fotemustine, cisplatin
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INTRODUCTION

AMONG ALL patients with non-small cell lung cancer (NSCLC), those presenting at diagnosis with evidence of metastatic disease in the central nervous system (CNS) are known to carry a very poor prognosis. In our experience [1], the median survival time of this group of patients is 4 months.

Although a precise evaluation of chemosensitivity has not been performed since these patients are generally excluded from phase II trials, only a few drugs are recognised as being active on NSCLC brain metastases. Among them are nitrosoureas and cisplatin, which is also considered as the most active compound in NSCLC overall.

Fotemustine is a recently synthetised nitrosourea which has also demonstrated substantial efficacy in NSCLC. At the time this study began, the response rate from the first French phase II trial was 12.5% when administered at a dose of 100 mg/m^2 on days 1, 8 and 15 in a series of 40 evaluable patients with squamous cell lung carcinoma [2]. The ability of nitrosoureas to pass the blood–brain barrier makes these compounds a potentially useful group of drugs for the treatment of central nervous system tumours. In fact, fotemustine has demonstrated substantial antitumour activity in brain metastases from malignant melanoma [3] as well as in malignant gliomas [4]. Interesting tumour regressions have also been observed with cisplatin alone on cerebral metastases from NSCLC [5].

The results of a phase II trial designed to evaluate the potential activity and toxicity of a combination of fotemustine and cisplatin in NSCLC patients with brain metastases are presented here.

PATIENTS AND METHODS

Patients

Patients were included between November 1990 and April 1993. All fulfilled the predefined main inclusion criteria: histologically proven NSCLC, no prior chemotherapy, Karnofsky index of 60% (or ECOG $\leq$ 2) and signed informed consent. Metastases to the CNS should not have been surgically removable; they did not have to be histologically proven but had to be bidimensionally measured on computed tomography (CT) scan. The protocol was approved by the local ethical committee.

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Treatment

The treatment plan consisted of induction chemotherapy (days 1 and 8: fotemustine 100 mg/m^2 in a 1-h bolus injection; days 1 and 22: cisplatin 120 mg/m^2 with 5 l hyperhydratation in 24 h, followed by maintenance chemotherapy in non-progressive patients (fotemustine 100 mg/m^2 and cisplatin 100 mg/m^2 every 3 weeks starting on day 50).

Evaluation of response

Cerebral metastases measurements were performed by CT scans, repeated on days 22 and 50 (at the end of induction therapy) and every 6 weeks during maintenance chemotherapy. Assessment of the primary tumour and other metastatic sites was made by chest X-ray and/or CT scans on the same dates.

Tumour response was evaluated using WHO criteria [6] by a panel of experts, including a medical oncologist, a neurologist and a radiologist, and was analysed separately for cerebral metastases and other tumour sites. Any response had to be confirmed on two successive evaluations in order to be registered. The duration of response was calculated from the date of first administration to the date of progression or last visit.

Evaluation of toxicity

Treatment toxicities were assessed using the WHO score every week during the induction period and every 3 weeks during the maintenance period, both clinically and biologically (serum electrolytes and creatinin, hepatic function tests and blood cells counts).

Statistical methods

The number of required patients evaluable for response and tolerance was calculated by using the method described by Gehan on the basis of an expected response rate of 20% with a beta risk of 0.05. The standard required error was 10%.

RESULTS

Patients' characteristics

31 patients were included. Their characteristics are given in Table 1. 2 patients were not evaluable for either response or toxicity because of early death (one acute intracranial hypertension and one pulmonary embolism). 4 additional patients had to be withdrawn from the study because of toxicity prior to the first evaluation and are, therefore, not evaluable for response. They include one patient with reversible grade IV gastrointestinal toxicity, one patient with reversible thrombocytopenia on day 6, and 2 patients with lethal infectious pneumonitis while in neutropenia (on days 31 and 40, respectively). Overall, 29 patients were evaluable for toxicity and 25 for response.

Table 1. Characteristics of the 31 included patients

		No. of patients
Sex	Male	28
	Female	3
Median age, years (range)		58 (35–71)
Karnofsky index	> 80%	13
	60–80%	18
Number of metastatic sites	0	8
(excluding brain)	1	17
	2	4
	3	2
Histological type	Epidermoid	17
	Large cells	10
	Adenocarcinoma	4
Previous treatment	None	24
(primary tumour)	Surgery alone	2
	Radiation alone	2
	Surgery and radiation	3

Table 2. Haematological toxicity (29 evaluable patients)

	WHO grade				
	0	I	II	III	IV
Anaemia (%)	21	41	28	10	0
Leucopenia (%)	31	21	14	31	3
Neutropenia (%)	34	17	14	21	14
Thrombopenia (%)	38	14	21	24	3

Response

An objective clinical response was observed in brain metastases in 7 (five partial and two complete responses) patients but was registered only in 2 patients. In the 5 remaining patients (all with partial responses), tumour regression on the CT scan was not maintained during the required 4 weeks: 3 presented with tumour progression on the following scan and the remaining 2, already mentioned, were considered as not evaluable for response because of early toxic death due to severe pneumonitis occurring during neutropenia. Overall, a documented clinical response was recorded in 4 patients (16%; 95% confidence interval 4–28%) and stable disease in 9 patients. In all 4 responding patients, the clinical response was considered partial in the primary lung tumour; in 2 of these the response was considered complete on brain CT scan on day 50. The histological type of responding patients was squamous cell carcinoma in 2 cases and undifferentiated large cell carcinoma in the remaining 2 patients. The duration of response, calculated from the date of first treatment to the date of progression, was respectively, 23, 21, 20 and 15 weeks in these 4 patients. The median duration of response was 20.5 weeks.

Survival

All patients have died and none were lost to follow-up. The median survival time was 16 weeks overall and the median survival time of the 4 responding patients was 28.5 weeks.

Toxicity

Haematological toxicity is presented in Table 2. Platelet transfusions were required in 3 patients and red blood cells in one. Grade I or II renal toxicity based on serum creatinine elevation was seen in 9 (31%) patients. As shown on Table 3, gastrointestinal toxicity was only severe on day 1 (24% grade III or IV).

Table 3. Gastrointestinal toxicity

	Total number of courses	WHO grade				
		0	I	II	III	IV
Day 1	30	16	2	5	5	2
Day 8	25	21	3	1	0	0
Day 22	22	17	1	2	2	0

The entire induction treatment was delivered in 14 of the 25 evaluable patients. In 4 patients, one injection had to be omitted either on day 8 or on day 22 and in 7 a 25% dose reduction was made on day 22. Seven of these 11 modifications were due to haematological toxicity (four neutropenias, three thrombopenias). Treatment delays due to haematological toxicity occurred in 57% of patients.

DISCUSSION

NSCLC is usually considered a weakly chemosensitive tumour. Although many agents have proven useful, the overall activity of the most efficient cisplatin-based combinations remains low and the response rates do not exceed 30%, mainly consisting of short-lasting partial tumour regressions. The median survival time is approximately 30 weeks in stage IV patients. Interestingly, a statistically significant survival advantage has been reported in patients receiving combination therapy compared to those receiving supportive care only [7]. Therefore, chemotherapy should be offered to most stage IV patients with acceptable general condition.

However, patients presenting with cerebral metastases represent a subgroup with a very poor prognosis and are generally not considered for chemotherapeutic treatment. Surgical removal of a solitary metastasis is controversial and may be offered to patients who have a good performance status, when the primary tumour is anticipated to be controlled locally [1]. Whole brain irradiation therapy may offer interesting palliation of symptoms in approximately 50% patients but the median survival is 15–18 weeks [8].

The efficacy of fotemustine single-drug chemotherapy in NSCLC initially reported by Le Chevallier and associates [2] has been confirmed since then in a larger trial: 13 of 77 (17%) patients presented evidence of tumour regression including 2 of 12 patients with evaluable brain metastases [9]. Furthermore, in a series of 28 patients with stage III or IV NSCLC treated with the combination of cisplatin and fotemustine, a 23% partial response rate was observed including 3 of 8 patients with cerebral metastases [10]. However, the results of a more recently published phase II trial on 37 evaluable patients were less encouraging since the overall response rate was only 13.5% [11].

In our study, 4 of the 25 evaluable patients (16%) presented evidence of partial tumour regression at the site of the primary tumour, 2 of which (8%) were simultaneously considered as complete responders on the brain CT scan. However, a documented but short-lived response on central nervous system metastases was observed in 7 patients. Like others [9], we found no response among patients with adenocarcinomas. The median duration of response was only 20.5 weeks and the median survival time 28.5 weeks for the four responders.

We observed marked haematological toxicity with this treatment. Two toxic deaths occurred during neutropenia and severe thrombocytopenia resulted in early treatment discontinuation in one case. A third of the patients experienced severe (WHO grade III or IV) haematological toxicity and treatment reports due to insufficient bone marrow recovery were performed at least once in half the patients. Twenty-four per cent of patients experienced grade III or IV gastrointestinal toxicity despite the systematic use of 5HT3 serotonin inhibitors together with cisplatin. The poor tolerance was probably at least partially related to the relatively bad general condition of this population of patients (50% presented with a Karnofsky index < 80% and 75% with at least one additional metastatic site). Overall, the toxicity of such a combination appears too high compared to the minor benefit to the patients.

This study has demonstrated the potential interest of fotemustine combined with cisplatin in the treatment of brain metastases from NSCLC. However, the limiting haematological toxicity prevents its recommendation as routine treatment in this setting.

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