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Cisplatin–Fotemustine Combination in Inoperable Non-small Cell Lung Cancer: Preliminary Report of a French Multicentre Phase II Trial

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Fotemustine is a new nitrosourea derivative whose activity has been demonstrated on metastatic melanoma with specific activity on brain metastases and also on poor prognosis lung cancers. Results of *in vitro* studies of a cisplatin–fotemustine combination seem promising. In order to evaluate the efficacy and safety of this combination, we performed two trials. 6 patients entered a preliminary study whose schedule was cisplatin 120 mg/m² on day 1 and fotemustine 100 mg/m² on days 1 and 8. 22 patients were enrolled in a second study which added 120 mg/m² cisplatin on day 22 followed by a 4-week rest period. In both trials, maintenance therapy consisted of cisplatin 100 mg/m² and fotemustine 100 mg/m² every 3 weeks until progression. Despite the poor prognostic factors which characterised our population (metastatic disease 86%, brain metastases 59%, ≤ 80% performance status 45%), the results remain attractive with a 23% partial response rate (29% in non-pretreated patients). Moreover, 3 out of 8 patients with evaluable cerebral metastases achieved a partial response (37.5%). Toxicity was mild and related to the cumulative dose of cisplatin (peripheral neuropathy and renal toxicity). We concluded that these results need to be confirmed in a randomised trial.
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INTRODUCTION

THE CONSISTENTLY poor prognosis of advanced non-small cell lung cancer (NSCLC) calls for new drugs or drug combinations to be tested such as the combination of fotemustine and cisplatin. Fotemustine is a new nitrosourea derivative with proven efficacy against metastatic melanoma [1], and specific activity on brain metastases [2]. Recent phase II studies showed that fotemustine was a potent drug when used alone in the treatment of NSCLC [3, 4]. Cisplatin is one of the most active single agents in NSCLC treatment. Its activity has also been observed in combination with other drugs and particularly with vinca alkaloids [5, 6]. *In vitro* studies of cisplatin–fotemustine combination in melanoma cell lines found this association to be more effective than fotemustine alone [7]. Moreover, both drugs cross the blood–brain barrier [2, 8].

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MATERIALS AND METHODS

From February 1989 to December 1990, two trials were performed in order to define the efficacy and safety of a cisplatin–fotemustine combination in NSCLC and, more specifically, in brain metastases.

6 patients were initially included in a preliminary study (Trial A). They received cisplatin 120 mg/m² on day 1 and fotemustine 100 mg/m² on days 1 and 8. As no major toxicity occurred, a second study (Trial B) was initiated which added to the first schedule a 120 mg/m² cisplatin administration on day 22 followed by a 4-week rest period. 22 patients entered this second study. In both trials, patients achieving a response or stabilisation received maintenance therapy consisting of cisplatin 100 mg/m² and fotemustine 100 mg/m² every 3 weeks until progression.

Eligibility criteria were histological evidence of NSCLC with

at least one measurable or evaluable indicator lesion, Karnofsky index > 60%, white blood cells > 4000/mm^3, neutrophils > 2000/mm^3, platelets > 150000/mm^3, serum creatinine < 130 μmol/l, proof of disease evolution within the 2 previous months, no more than one prior chemotherapy treatment, no previous cisplatin or cisplatin analogue treatment, no chemotherapy during the last 4 weeks (6 weeks for prior nitrosourea chemotherapy treatment) and written informed consent. The studies were conducted according to the Declaration of Helsinki, and approval for the study was obtained from local ethics committees.

Fotemustine was administered as a 1-h intravenous infusion in 250 ml of 5% glucose solution and protected against daylight. Cisplatin was given as a 3-h infusion in 3% saline solution together with a 5 l hydration over 24 h.

Response was assessed at the first maintenance cycle on day 50 and thereafter every two maintenance cycles. Response and toxicity were evaluated according to the WHO criteria [9]. All the responses have been reviewed by a panel of investigators.

Patients' characteristics are shown in Table 1. Among the 22 patients enrolled in Trial B, 19 had metastatic disease. 4 had one disease site, 6 had two sites, 9 had three sites and 3 patients had four or more sites. 13 patients had brain metastases. 10 patients had ≤ 80% performance status. 8 patients had received prior chemotherapy including 6 patients who had received vinorelbine as monochemotherapy.

Table 1. Patients' characteristics

	Trial A	Trial B
No. of evaluable patients	6	22
Male/female	6.0	19.3
Age (years)		
Median	51	58
Range	36–62	36–71
UICC classification		
Stage III	2	3
Stage IV	4	19
Performance status		
Median	80	90
Range	70–90	60–100
Disease sites		
Lung	6	21
Bone	1	1
Lymph nodes	2	11
Liver	2	4
CNS	3	13
Adrenal glands	0	3
Pleural	0	3
No prior chemotherapy	5	14
No prior treatment	4	10
Brain surgery + RX	0	2
Brain RX	0	2
Lung surgery	1	0
Prior chemotherapy	1	8
Alone	0	7
Surgery + RX + CT	0	1
Brain RX	1	0
Cell type		
Adenocarcinoma	3	9
Squamous cell	2	4
Large cell	1	9

RX, radiotherapy; CT, chemotherapy.

RESULTS

All 28 patients treated in the two trials received 100% of the scheduled doses. Only one second fotemustine administration was delayed because of performance status degradation and vomiting related to the first treatment. Maintenance therapy was administered to 15 patients (seven cycles in 4/6 patients for Trial A and 35 cycles in 11/22 patients in Trial B). However, 1 patient with partial response with brain metastases had to stop cisplatin after four maintenance cycles because of paresthesia. Fotemustine was then given alone for three additional courses until progression, without any complication.

No objective response was observed among the first 6 patients (three stable diseases and three progressions). In Trial B, 5 patients achieved a partial response (23%, 95% confidence interval 5–40), 6 had stable disease and 11 had progressive disease (Table 2). Partial response rate in patients who had not received prior chemotherapy was 29% (4/14). 8 patients had evaluable and previously untreated brain metastases. 3 of them achieved a partial response in this site (37.5%).

Median duration of response was 31 weeks (range 20–51) but this was probably underestimated. One patient had to stop his treatment after the fifth maintenance course because of paresthesia; when chemotherapy was followed by brain or lung radiotherapy or both, response duration to cisplatin–fotemustine was calculated until the beginning of radiotherapy.

During Trial A, no haematological, renal or hepatic toxicity occurred which was related to the first cycle. Despite prophylactic anti-emetic treatment, there were 2 grade 1, 2 grade 2 and 2 grade 3 cases of nausea-vomiting related to the cisplatin–fotemustine combination. No vomiting occurred when fotemustine had been given alone on day 8.

The main toxicities in Trial B were haematological (Table 3) and gastrointestinal (Table 4). During the first cycle there were two grade 2 thrombocytopenia (nadir day 36), one grade 2 and one grade 3 leucopenia (nadir day 33). There was also one grade 4 leucopenia with neutropenic-related fever. Gastrointestinal toxicity was only partially prevented by prophylactic anti-emetic treatment given before cisplatin. Thirty-five cisplatin administrations were evaluated. There were 3 grade 2 and 2 grade 3 cases of vomiting. Fotemustine alone was usually given without anti-emetic treatment and one grade 1 and one grade 2 occurred.

Maintenance therapy (Table 5) was associated with leucopenia in 2 patients, thrombocytopenia in 2 patients and anaemia in all patients. Grade 1 or 2 neurological toxicity occurred in 3 patients who had received more than a total dose of 600 mg/m^2 of cisplatin. In 2 cases, the treatment was stopped. 2 patients had a grade 1 serum creatinine increase after the same cisplatin dose.

Table 2. Responses

	Trial A	Trial B
Responders	0	5
Stage IV	0	5
No prior chemotherapy	0	4
Prior chemotherapy	0	1
Type of response		
Complete response	0	
Partial response	5	
Stable disease	6	
Progressive disease	11	

Table 3. First treatment haematological toxicity (including J1, J8 and J21) for Trial B

Toxicity	Grade				
	0	1	2	3	4
Anaemia	10 (45.5%)	6 (27.3%)	4 (18.2%)	2 (9%)	0 (0%)
Leucopenia	10 (45.5%)	9 (41%)	1 (4.5%)	1 (4.5%)	1 (4.5%)
Neutropenia	13 (59.1%)	6 (27.3%)	1 (4.5%)	1 (4.5%)	1 (4.5%)
Thrombocytopenia	19 (86.4%)	1 (4.5%)	2 (9%)	0 (0%)	0 (0%)

Values expressed are no. of patients (%).

Table 4. Gastrointestinal toxicity for Trial B

Treatment	No. of cures	No. of cures with anti-emetics	Grade					
			0	1	2	3	4	NE
J1	22	22	18	1	2	1	0	0
J8	22	2	19	1	1	0	0	1
J21	22	20	11	0	1	1	0	9

NE, non-evaluated cures.

DISCUSSION

Main combination chemotherapy schedules show a 17–54% response rate when used in randomised studies [10–13]. Patients who enter these trials usually have good prognostic factors including no prior chemotherapy, no brain metastases and a good performance status.

Cisplatin–fotemustine combination, with a 23% response rate (29% in non-pretreated patients), remains a promising treatment regarding the poor prognostic factors of the population: 86% of the patients had metastatic disease, 59% had brain metastases, and 45% had ≤ 80% performance status. Moreover, 3 out of 8 patients with evaluable brain metastases achieved a partial response. Some schedules (high dose cisplatin or etoposide) have been reported to achieve a better response rate on brain metastases, but were associated with higher toxicity and in some cases, neutropenic-related deaths [8, 14].

In conclusion, a cisplatin–fotemustine combination when given to metastatic NSCLC, seems to be safe and interestingly active, especially on brain metastases. The limiting toxicity of this schedule appears to be related to the cumulative cisplatin dose and includes peripheral neuropathy and renal toxicity, whereas haematological toxicity remains mild. These results need to be confirmed by a randomised trial which will compare in patients with NSCLC and brain metastases, a standard arm treatment versus cisplatin–fotemustine combination.

Table 5. Maintenance therapy haematological toxicity

Toxicity	Grade					
	0	1	2	3	4	NE
Anaemia	13	10	6	0	0	6
Leucopenia	26	1	1	1	0	6
Neutropenia	27	2	0	0	0	6
Thrombocytopenia	23	4	2	0	0	6

NE, non-evaluated cures. Values expressed are no. of cures.

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Management of Breast Cancer in the Elderly

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The management of breast cancer in elderly women was analysed by a retrospective study of 150 women over 70 years old referred to our department between 1984 and 1988. 80 were T1-T2, 33 were T3 and 34 were T4. 107 were N0 and 43 were N1-N2. 16 women (11%) were in poor health, preventing conventional treatment. Treatment choice varied with age: 60% of the women aged 70–79 (group 1) and 23% of the oldest women (group 2) were treated conventionally. The use of surgery decreased with age and surgical procedures were conventional in only 85% of the group 1 women and in 56% of the group 2 women. Definitive radiation therapy was used more frequently in the oldest women, as was primary hormone therapy. Quality of follow-up also varied with age. Five-year survival rates were still high in both groups while relapses were frequent. Breast cancer was consequently a frequent cause of death. The increase in the proportion of elderly people with breast cancers over the next few years will require validated guidelines. Specific protocols and specific rules of management must be drawn up.

Key words: breast cancer, elderly, surgery, radiotherapy, hormone therapy
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INTRODUCTION

AGE IS one of the principal risk factors for breast cancer. The incidence of breast carcinoma increases with age to over 300 per 100 000 woman-years in women over 70 years old [1]. Thirty per cent of the new cases diagnosed in France are aged over 70 [2]. In western countries, this proportion is increasing as life expectancy grows. The percentage of elderly women treated for breast cancer was greater between 1968–1978 than between 1958–1968 [3]. Breast carcinoma is a major health problem in the elderly but retrospective studies have shown that treatment varies according to the patient's age and is often less intensive in old patients [4–7]. This may be because breast carcinoma is often accompanied by other medical problems that may contraindicate aggressive treatment, such as surgery or radiotherapy. Nevertheless, there may be other subjective reasons. Breast adenocarcinoma is thought to be a slow growing cancer in elderly patients, with no imperative need for conventional treatment. It has also been said that these patients do not accept aggressive treatment, that they are often indifferent to cancer and not concerned with breast preservation. This could lead to sub-optimal treatment. Breast carcinoma is a major problem, and even early breast carcinoma is a major cause of death in women aged over 65 [3, 8, 9]. A 70-year-old woman has a life expectancy of 16 years in western countries, and an 85-year-old woman can expect to live 7 years [9]. Since 95% of tumour relapses occur in the first 4 years after treatment, local-regional control must be a major concern for physicians, even in the oldest patients [10]. While there is evidence that local regional control of breast cancer is needed in both elderly and younger women, the general frailty of the elderly plus the health of each individual must be taken into account. This may require a wide range of treatments, some of them unconventional. The validity of some of these unusual therapeuties has not been demonstrated, and physicians lack guidelines because few data are available. Clinical trials targeting this population are rare [11]. Most trials exclude older women and specific data mainly come from retrospective studies of selected elderly populations. Moreover, comparison between treatments in terms of overall survival and disease-free survival

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