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Fotemustine Plus Dacarbazine for Malignant Melanoma

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119 patients with metastatic melanoma received fotemustine 100 mg/m² on days 1 and 8 and dacarbazine 250 mg/m² on days 15–18. After a 5-week rest, fotemustine 100 mg/m² on day 1 and dacarbazine 250 mg/m² on days 2–5 was given every 3–4 weeks. 12 complete responses (11.6%) and 16 partial responses were observed in 103 evaluable patients (response rate 27.2%). The median duration of response was 21.5+ weeks (8+ to 53+). The response rate was 26.3% in CNS, 18.2% in visceral sites and 37.5% in non-visceral sites. The toxicity was mainly haematological: grade III–IV leukopenia in 27.4% and thrombocytopenia in 23.4%. The response rate was lower than that in 63 patients previously reported. The present series had a higher median age (54 vs. 40 years) without any differences in other population variables. However, activity on CNS metastases and on non-visceral sites was confirmed. Haematological toxicity was about 50% lower than that with fotemustine alone. Hence, this is an active outpatient regimen for metastatic melanoma, especially against cerebral and non-visceral metastases.
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INTRODUCTION

MALIGNANT MELANOMA is a rare but very aggressive tumour, since it is responsible for 65% of skin cancer deaths [1]. When distant metastases appear, the survival expectancy of the patients drops dramatically to a few months [2]. At this stage of the disease, surgery is very rarely curative [3] and radiotherapy is only palliative [4, 5].

Many mono- as well as polychemotherapeutic regimens have been tested, but melanoma does not belong to the very chemosensitive tumours. To date the drug of reference is dacarbazine, with an average response rate of 20% [6] in monotherapy. It is active on non-cerebral metastases and is poorly tolerated with regards to nausea and vomiting. Few other drugs are efficient in the treatment of melanoma. Response rates of 15–17% have been observed with nitrosoureas [7, 8]. Fotemustine is a new drug of this class. Its activity against disseminated malignant melanoma has been demonstrated in a large phase II trial including 153 evaluable patients [9]. The overall response rate was 24.2% (17.4–31.0%: 95% confidence interval). Especially interesting were the responses observed on cerebral metastases: 25.0% [10] and the good tolerance of the drug. Dacarbazine is not cross-resistant with fotemustine and has a different toxicity and mechanism of action, though it is also an alkylating agent.

A phase II trial combining these two drugs was then initiated in May 1988, aimed at obtaining a higher response rate. The first results on 63 patients were recently reported [11]. The response rate was 33.3%: 28.6% on cerebral sites, 23.1% on visceral lesions and 43.3% on non-visceral metastases. The median duration of response was 19+ weeks ranging from 8+ to 34+ weeks. The toxicity was moderate and mainly haematological: 22.2% grade III–IV leukopenia and 20.3% grade III–IV thrombocytopenia. This trial was continued and we report here the final results on 103 evaluable patients.

PATIENTS AND METHODS

Patients

119 patients have been included between May 1988 and October 1989. 16 were not evaluable for response (10.6%). The reasons for non-evaluation were: early death without evaluation: 4; early death and uncomplete therapy: 3; protocol violation: 6; and lost to follow-up: 3. The biometric parameters of the 103 evaluable patients were: sex ratio: 0.98 (51 men/52 women); median age: 54 years (range 19–79); median performance status index: 90% (range 60–100%) according to the Karnofsky scale.

The primary melanomas were located on the lower limbs (33/103), the trunk (18/103), the head and neck (18/103), the upper limbs (10/103) or was not specified in 24/103 cases. All were histologically confirmed melanomas, 5 from choroïdal origin and 98 from cutaneous origin.

The prior treatments of the patients consisted of surgery in 90 cases and radiotherapy in 7 cases. Only 15 patients had previously received chemotherapy and only one of them more than one regimen.

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The sites and numbers of the metastases were as follows: central nervous system (CNS): 19; liver: 28; lung: 23; other visceral lesions: 7; lymph nodes: 35; skin: 38; other non-visceral lesions: 10. The patients can be classified according to the dominant metastatic site, i.e. with the main influence on the vital prognosis: CNS: 19 patients; visceral site: 44; non-visceral site: 40.

Treatment

An induction cycle was first administered consisting of: fotemustine 100 mg/m^2 days 1 and 8, dacarbazine 250 mg/m^2 days 15–18 followed by a 5-week rest period. For stabilised or responding patients, a maintenance treatment was given: fotemustine 100 mg/m^2 on day 1 and dacarbazine 250 mg/m^2 on days 2–5 every 3 weeks. This was continued until a disease progression or an unacceptable toxicity occurred. Fotemustine and dacarbazine were both administered as a 1-h intravenous infusion protected from daylight and diluted in 250 ml 5% glucose for fotemustine and 9% NaCl for dacarbazine.

Design of the investigations

The response was assessed at the end of the 4th and 8th weeks of the induction cycle and before each maintenance cycle. The tumour response was evaluated on measurable lesions [brain computer tomography (CT) scan for cerebral lesions, radiography, ultrasound (USS) or CT scan for visceral lesions and clinical examination for superficial lymph nodes or skin metastases] according to WHO criteria. Differential blood cell count, liver function tests [aspartate, alanine amino transferase (AST, ALT), alkaline phosphatases, bilirubin], blood urea nitrogen and serum creatinine were performed weekly during the induction cycle and before each maintenance cycle.

RESULTS

Tumour responses

Among the 103 evaluable patients, 12 (11.6%) complete responses (CR) and 16 partial responses (PR) were observed, leading to an overall response rate of 27.2%. There were also four minor responses (MR), 20 stabilisations (ST) and 51 progressions (PD).

The median duration of the objective responses (CR and PR) was 21.5 weeks (range 8+ to 53+). The median survival time of the whole population was 13+ weeks (8+ to 54+) reaching 43.5 weeks (8+ to 54+) for the responders. For complete responders, median duration of responses was 27.5 weeks (16+ to 52+) and median survival time 47 weeks (21+ to 52+).

The responses according to the metastatic sites are detailed in Table 1. According to the dominant metastatic site, 26% responses (2 CR + 3 PR out of 19) for patients with CNS lesions, 18% (2 CR + 6 PR out of 44) in cases of visceral metastases and 38% (8 CR + 7 PR out of 40) in cases of non-cerebral and non-visceral metastases were reported.

No difference in the response rate (RR) between the pretreated and the non-pretreated patients (29 and 26%, respectively) was noted.

Toxicity

The main toxicity was a moderate myelosuppression that is detailed in Table 2. According to the WHO classification the frequency of grade III–IV leukopenia with a median nadir on

Table 1. Responses according to the metastatic sites

	Metastatic target		
	Number of evaluated lesions	Number of CR + PR	Response rate/ evaluated lesions (%)
CNS	19	3 + 3	31.6
Liver	28	1 + 3	14.3
Lungs	23	1 + 2	13.0
Other visceral metastases	7	0 + 1	14.3
Overall visceral metastases	58	2 + 6	13.8
Lymph nodes	35	5 + 3	22.8
Skin	38	6 + 8	36.8
Other non-visceral metastases	10	0 + 2	20.0
Overall non-visceral metastases	76	11 + 13	31.6

CR, Complete response; PR, partial response.

Table 2. Haematological toxicity according to WHO classification

	Grade					No. of evaluated patients
Blood cells	0	I	II	III	IV	
Haemoglobin	49	16	8	7	1	81
(%)	(60.5)	(19.8)	(8.9)	(8.6)	(1.2)	
Leucocytes	20	17	21	19	3	80
(%)	(25.0)	(21.3)	(26.3)	(23.7)	(3.7)	
Neutrophils	26	12	10	21	10	79
(%)	(32.9)	(15.3)	(12.6)	(26.6)	(12.6)	
Platelets	35	14	13	13	6	81
(%)	(43.2)	(17.4)	(16.0)	(16.0)	(7.4)	

Table 3. Liver function tests modifications

Grade		Enzyme			
Entry into the study	Maximum during the study	Aspartate amino-transferase	Alanine amino-transferase	Alkaline phosphatases	Bilirubin
0	0	47	38	37	56
0	I	7(3*)	11(5*)	12(4*)(2†)	3(1*)
0	II	2	4(1*)	4(3*)	0
I	II	2(1*)	4(4*)	4(2*)	0
0	III	1	2	0	0
I	III	1(1*)	1	2(2*)	0
0	IV	0	1	0	0
I	IV	0	2(1*)	0	0
III	IV	1	0	0	0
Total no. of evaluated patients		61	63	59	59

* Number of patients with liver metastases.
† Number of patients with liver and bone metastases.

Table 4. Comparison of monotherapy and the combined regimen

	Fotemustine $n = 153$	Fotemustine + dacarbazine $n = 63$	Fotemustine + dacarbazine $n = 103$
Sex ratio	76 M/77 F = 0.98	31 F/32 M = 0.97	51 M/52 F = 0.98
Median age (Range)	54 years (20–80)	40 years (19–78)	54 years (19–79)
Median Karnofsky Index (range)	90 (60–100)	90 (60–100)	90 (60–100)
Previous chemotherapy (%)	59.5	31.7	14.5
Dominant metastatic site (%)			
CNS	23.5	11.1	18.4
Visceral	47.7	41.3	42.7
Non-visceral	28.8	47.6	38.2
Response rate (%)	3 CR + 34 PR (24.2)	9 CR + 12 PR (33.3)	12 CR + 16 PR (27.2)
Complete response rate (%)	2.0	14.2	11.6
Median duration of response in weeks (range)	22 (7–80)	19 + (8+–34+)	21.5+(8+–53+)
Response rate according to the dominant metastatic site (%)			
CNS	25.0	28.6	26.3
Visceral	19.2	23.1	18.2
Non-visceral	31.8	43.3	37.5
Haematological toxicity (%)			
Grade III–IV leukopenia	46.3	22.2	27.4
Grade III–IV thrombopenia	40.3	20.3	23.4
Hepatic enzymes evaluation (%)			
Aspartate amino transferase Grade II–III	12.0	4.5	9.8
Aspartate amino transferase Grade IV	2.3	4.5	1.6
Alanine aminotransferase Grade II–III	17.4	8.7	17.4
Alanine aminotransferase Grade IV	5.3	—	4.7
Alkaline phosphatase Grade II–III	16.8	—	10.2
Alkaline phosphatase Grade IV	1.6	—	—

Nausea and vomiting

	Fotemustine	Dacarbazine	Fotemustine	Dacarbazine
Grade 0–I	71.4%	63.2%	47.6%	66.5%	58.0%
Grade II–III	28.2%	36.0%	52.4%	32.9%	41.9%
Grade IV	0.4%	0.7%	0%	0.6%	0%

n, Number of patients; M, male; F, female; CR, complete response; PR, partial response.

day 42 (7–56) and 23.4% grade III–IV thrombocytopenia with a median nadir on day 34 (3–42).

Nausea and vomiting were the other side-effects. They were evaluated in 176 fotemustine and 81 dacarbazine administrations. There were, respectively, 51.7 and 38.3% grade 0, 40.9 and 50.6% grade I–II, 7.5 and 11.0% grade III–IV. This toxicity was acceptable.

In few cases a moderate and transient increase in hepatic enzymes was noted. Data are detailed in Table 3. ASAT raised to a grade III or IV in 3 cases (4.9%), ALAT in 6 cases (9.5%) and alkaline phosphatases raised to grade III in 2 cases (3.4%). There was a concomitant elevation of two parameters in 11 patients (in 3 cases one of the enzymes reached grade III) and of three parameters in 7 patients (in 4 cases one or two parameters reached the grade III or IV). These elevations were always rapidly reversible when they were not related with a disease progression.

No renal toxicity nor any other meaningful side-effect have been observed. There was no treatment disruption due to toxicity.

DISCUSSION

The evaluation on the first 63 patients and the actual one on 103 patients are presented in Table 4 and compared with the results of the phase II study on 153 patients, where fotemustine was given alone [9]. It is important to note that fotemustine in monotherapy was given on days 1–8–15 at the dose of 100 mg/m^2 during the induction cycle and at the same dose on day 1 every 3 weeks in the maintenance cycles. Therefore, in the combined

study, the dose of fotemustine in the induction cycle was reduced (200 mg/m^2 instead of 300 mg/m^2).

In the interim report the response rate seemed to be higher than with fotemustine alone (24.2 and 33.3%, respectively). The activity on cerebral metastases was maintained and there was a high response rate among the patients with non-visceral lesions (43.3%). The haematological toxicity was about 50% inferior to the one observed with fotemustine alone.

In this final evaluation on 103 patients the response rate dropped to 27.2% but the complete responses remain more frequent (11.6%) than with fotemustine alone (2.0%). The median duration of response is stable around 20 weeks in the three series. The CNS metastases still respond well (26.3% objective responses) with this combined regimen despite the suppression of 100 mg/m^2 fotemustine in the induction cycle when compared to the monotherapy. It should be noted that 59.5% of the monotherapy patients were pretreated while only 14.5% of the 103 patients were. This may have had an influence on the response rates. There seems to be no advantage of the combined treatment for visceral lesions but non-visceral lesions appear to respond better even if it is less obvious in the 103 patients than in the first 63.

The haematological toxicity remains as low among the 103 patients as it was among the first 63. This is well correlated with the lower total dose of fotemustine, which is the only haematotoxic drug, in the combined treatment. However, the median onset, nadir and normalisation days do not change despite the suppression of the third fotemustine administration in the combined schedule. For leukopenia they occur on median days 41, 44 and 53 in the monotherapy and on median days 36, 42 and 54 in the combined regimen, respectively. For thrombocytopenia they are on median days 29, 35 and 45 in the monotherapy and on median days 29, 34, 42 in the combined regimen, respectively.

Fotemustine-related nausea and vomiting are moderate in both regimens and slightly heavier with dacarbazine in the combined protocol. The hepatic toxicity is equally low with the two regimens.

No obvious difference in terms of biometric parameters, prognostic factors or prior treatments between the interim and the final evaluation of the combination, except for the median age of the patients, could explain the lower response rate.

Many combined chemotherapeutic regimens have been tested and reported. Most of the protocols include dacarbazine and are three drug therapies. Very few are randomised, and most studies concern small samples of patients (20–60 patients). If we consider protocols containing both dacarbazine and a nitrosourea, response rate (RR) varies from 15 to 47% (12, 13, 14, 15, 16, 17, 18), only three of this series concerned numbers of patients higher than 100 [13, 15, 16] and obtained 15, 22 and 28% RR, respectively. The median durations of response range between 3.5 and 7.5 months. Some other trials contain a nitrosourea, alone or combined with a non-dacarbazine drug [17, 19–21]. The RR range from 30.0 to 48.0% but the series are very small: 9–42 patients. The median durations of response are short: 2–4.5 months. Other regimens containing no nitrosourea give various RR from 2.5 to 25.0% [22, 23, 17].

A review of the literature shows that complete RR vary from 0 to 13.0% and overall RR from 2.5 to 48%. The highest RR are observed in the smallest series. The durations of response range from 2 to 7.5 months and few studies give information on survival. The present series is large (103 patients), with a response rate that remains superior to 25% and a median duration of response that is among the longest reported.

In conclusion, this study confirms the efficacy of fotemustine in the treatment of disseminated malignant melanoma in a large series of patients, and particularly its activity on cerebral metastases. The combination with dacarbazine seems especially efficient on skin and lymph node metastases and is equally active on visceral and cerebral lesions as the monotherapy, but it is less haematotoxic, well tolerated and can be given safely on an outpatient basis.

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Melphalan Concentration and Distribution in the Tissues of Tumour-bearing Limbs Treated by Isolated Limb Perfusion

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Levels of melphalan (L-phenylalanine mustard) were measured in the tissues of tumour-bearing limbs treated by isolated limb perfusion (ILP). 41 samples of melanoma tissue, normal fat and skin were excised from 15 patients during ILP. A high performance liquid chromatography assay was used to measure melphalan concentrations. Levels of melphalan were higher in tumour than in fat ($P < 0.01$, Wilcoxon signed-ranks test), and not significantly different from levels in adjacent skin. In 2 cases there was significant regional toxicity in the treated limb, but this was not related to the levels of melphalan measured in the tissues of the limb. It is encouraging that the concentrations of melphalan which were achieved in large necrotic nodules by ILP were similar to those in well-perfused normal skin.
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INTRODUCTION

ISOLATED LIMB perfusion (ILP) is a form of regional chemotherapy for cancer which involves the exposure of a tumour-bearing limb to a high concentration of anticancer agent, while sparing the patient from systemic toxicity. In the management of malignant melanoma, ILP with melphalan is an effective method of control for locoregional advanced disease, and may be an effective adjuvant to surgery in the treatment of high-risk primary lesions [1]. Melphalan is a bifunctional alkylating agent which acts on tumour cell DNA. The drug must therefore penetrate tumour masses in order to be effective.

It has been shown that ILP can successfully achieve high levels of melphalan in the perfusate which circulates within the treated limb, with low levels in the systemic circulation [2, 3], but there have been no published studies to show how melphalan distributes within the tissues of the tumour-bearing limb during ILP.

The aim of this study was to measure the levels of melphalan in the tissues of tumour-bearing limbs treated by ILP.

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PATIENTS AND METHODS

Clinical method of ILP

External iliac ILP of the lower limb for malignant melanoma was performed by a method based on standard techniques [4, 5]. Fluorescein is added to the perfusate and observation with ultraviolet light confirms adequate perfusion and satisfactory isolation. Melphalan was given in a dose of 1.75 mg/kg body weight, when the calf skin temperature reached 37.5°C. ILP lasted 1 h, according to our protocol for therapeutic perfusion. The flow of perfusate was adjusted to the maximum achievable rate during ILP.

Samples of perfusate were drawn at 5-min intervals for melphalan assay by high performance liquid chromatography (HPLC). The area under the perfusate concentration–time curve (AUC) for each patient was derived by the trapezoidal rule.

Ethical Committee approval was obtained for blood and tissue sampling. All patients gave informed consent for the procedures.