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Chemotherapy by fotemustine in cerebral metastases of disseminated malignant melanoma*

Claude Jacquillat[1], David Khayat[1], Pierre Banzet[2], Maryse Weil[1], Marie-Francoise Avril[3], Pierre Fumoleau[4], Moïse Namer[5], Jean Bonneterre[6], Pierre Kerbrat[7], Jean-Jacques Bonerandi[8], Roland Bugat[9], Philippe Montcuquet[10], Bruno Audhuy[11], Didier Cupissol[12], Richard Lauvin[13], Edouard Grosshans[14], Catherine Vilmer[15], Chantal Prache[1], and Jean-Pierre Bizzari[1]

Oncology departments of [1]Hôpital Pitié-Salpêtrière, Paris; [2]Hôpital St. Louis, Paris; [3]Institut G. Roussy, Villejuif; [4]Centre R. Gauducheau, Nantes; [5]Centre A. Lacassagne, Nice; [6]Centre O. Lambret, Lille; [7]Centre E. Marquis, Rennes; [8]Hôpital Ste Marguerite, Marseille; [9]Centre C. Regaud, Toulouse; [10]CHU de Besançon; [11]CHU Pasteur, Colmar; [12]Centre Val d'Aurelle, Montpellier; [13]Hôpital Sud, Rennes; [14]Hôpital Civil, Strasbourg; [15]Centre R. Huguenin, St. Cloud, France

Summary. A total of 42 patients with cerebral metastases of malignant melanoma were included in this study of the nitrosourea fotemustine. The treatment plan consisted of a 1-h i.v. infusion of 100 mg/m^2 fotemustine every week for 3–4 weeks, followed by a 4- to 5-week rest period. Responding or stabilised patients then received 100 mg/m^2 fotemustine every 3 weeks. Among the 39 evaluable patients, 2 complete responses and 9 partial responses were documented, leading to an overall response rate of 28.2%. Most of the responses were obtained in previously untreated patients and/or those presenting with a single cerebral metastasis. Toxicity was mild and mainly hematological, especially in patients previously treated by polychemotherapeutic regimen. Our study confirms the activity of fotemustine in cerebral metastases of disseminated malignant melanoma.

Introduction

Brain metastases of malignant melanoma are a very poor prognostic factor [1, 2]; without treatment, the median duration of survival ranges from 3 to 4 weeks, with a slight increase to 6–8 weeks in patients receiving corticotherapy [12, 16, 17], although there is no statistical evidence that corticosteroids prolong survival. The main treatment is surgery, sometimes combined with radio- or chemotherapy; the treatment chosen depends on the site and the extent of disease [5]. Surgery is mostly indicated in patients showing a single cerebral metastatic site, with few (if any) extra-cerebral metastases and with a good performance status [4, 11]. Encephalic radiotherapy represents a palliative treatment that is still controversial due to the usual radioresistance of this tumor [16, 17]. Systemic chemotherapy has rarely been used in the treatment of brain metastases from malignant melanoma, and clinical trials are very rare because brain metastases are most often excluded from therapeutic protocols due to the lack of activity of most drugs against them. We recently reported the activity of a new nitrosourea, fotemustine, in disseminated malignant melanoma [3, 7]; the drug showed promising activity against cerebral metastases [8], which led us to initiate a phase II study.

Patients and methods

From December 1985 until May 1988, 42 consecutive patients showing cerebral metastases of histologically confirmed melanoma were included in this multicentre study. Inclusion criteria were: the presence of one or more measurable or evaluable lesion, evolutive evidence of the lesion, a life expectancy of >4 weeks, correct hematological status and an interval of 4 weeks since prior chemotherapy. Patients were treated with fotemustine according to the following plan: induction therapy of 100 mg/m^2 every week for 3–4 consecutive weeks, followed by a 4- to 5-week rest period; then maintenance therapy of 100 mg/m^2 fotemustine was carried out every 3 weeks in responding or stabilised patients. Fotemustine – a new amino acid-linked nitrosourea characterised by a phosphonoalanine carrier group grafted to the nitrosourea radical – was given in 5% glucose as a 1-h i.v. infusion, protected from light.

Clinical, biological and radiological check-ups (brain CT scan) were carried out during the week before the first administration, and evaluation of drug activity was done at week 4 and/or 8 during both the induction therapy and every one or two courses of maintenance therapy. Activity and toxicity were scored according to WHO criteria. Objective responses were defined as follows: complete response, the disappearance of all lesions; partial response, a decrease of $\geq 50\%$ in the sum of the product of the longest perpendicular diameters of the target lesions; stabilisation, a decrease or increase of $\leq 25\%$ in the same; and progressive disease, an increase of $\geq 25\%$ in any indicator lesion. Informed consent was obtained from all patients. Statistical analysis of survival curves was carried out by the Kaplan-Meyer method, and comparison of survival was calculated by log-rank tests.

* Others institutions involved in this trial: A. Bernadou, Hôtel Dieu, Paris; J. Clavier, CHR de Brest; M. Delaunay, Hôpital Pellegrin Tripode, Bordeaux; J. P. Escande, Hôpital Tarnier, Paris; P. Fargeot, Centre George François Leclerc, Dijon; P. Lauret, Hôpital Charles Nicolle, Rouen; R. Leblay, Hôpital Sud, Rennes; P. Litoux, CHR de Nantes; G. Lorette, Hôpital Trousseau, Tours; R. Metz, Centre Alexis Vautrin, Nancy; A. Monnier, CHR Boulloche, Montbelliard; M. Mousseau, CHR de la Tronche, Grenoble; J. P. Olivier, Hôpital Dupuytren, Limoges; R. Touraine, Hôpital Henri Mondor, Créteil; F. Truchetet, Hôpital de Thionville, France

Offprint requests to: Claude Jacquillat, Service d'Oncologie, Médicale, Pavillon Jacquart, Hôpital Pitié Salpétrière, 47 bd de l'Hôpital, F-75651 Paris Cedex 13, France

Table 1. Patient characteristics

Characteristics	Patients (*n*)
Evaluable patients	39
Men/women	19/20
Median age (year)	49
Range	(26 – 72)
Median Karnofsky performance status	90%
Range	(60% – 100%)
Metastatic site:	
Cerebral alone	16
Cerebral + extra-cerebral	23
Cerebral metastases:	
Single	13
Multiple	26
Prior chemotherapy:	
None	16
One regimen	18
Two or more regimens	5

Table 2. Characteristics of response

Response:	
Complete	2
Partial	9
Stabilisation	9
Progressive disease	19
Response rate:	28.2%
No prior chemotherapy	50%
Prior chemotherapy	13%
Median duration (weeks)	11
Range	8 – 102 +
Overall survival (weeks)	26
Range	4 – 146 +
Median survival (weeks):	
Responders (range)	51 (11 – 102 +)
Non-responders (range)	15 (14 – 146 +)
1-year survival	21%

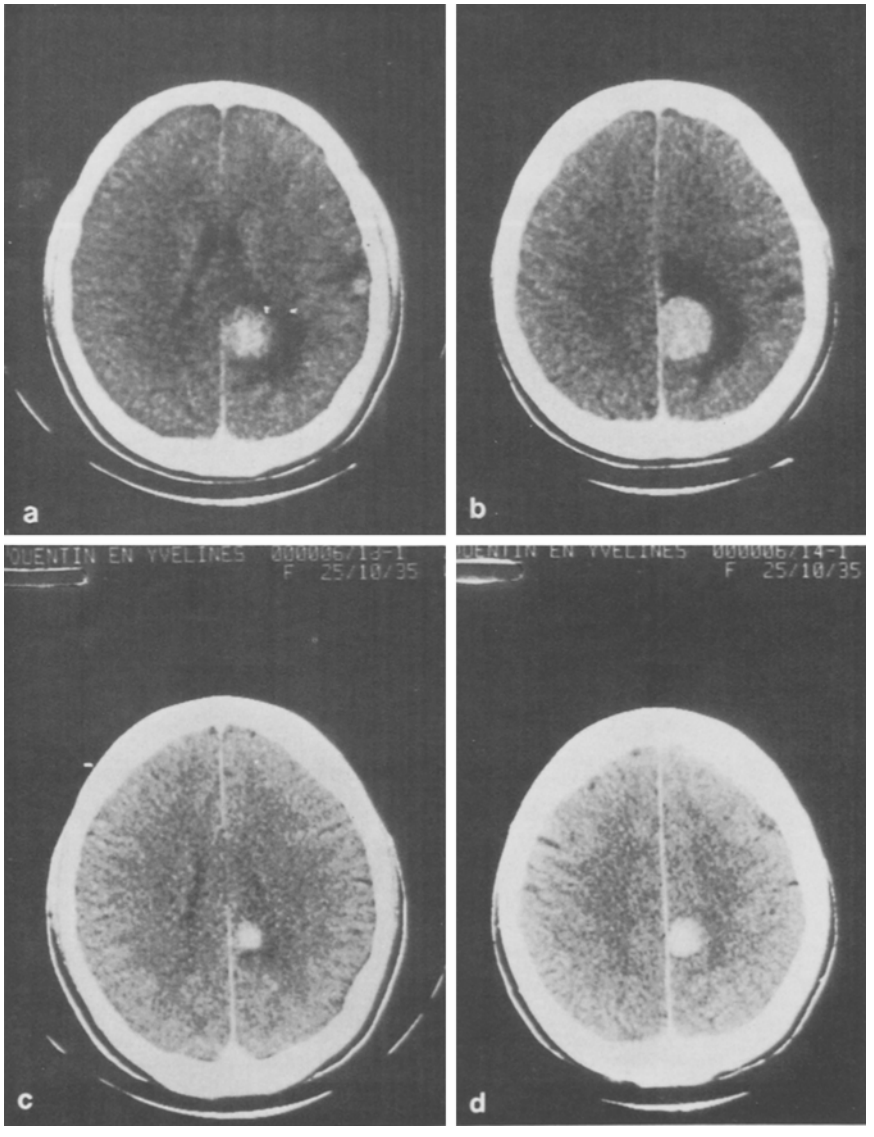

Fig. 1. Partial response in cerebral metastasis (duration of response, 11 weeks)

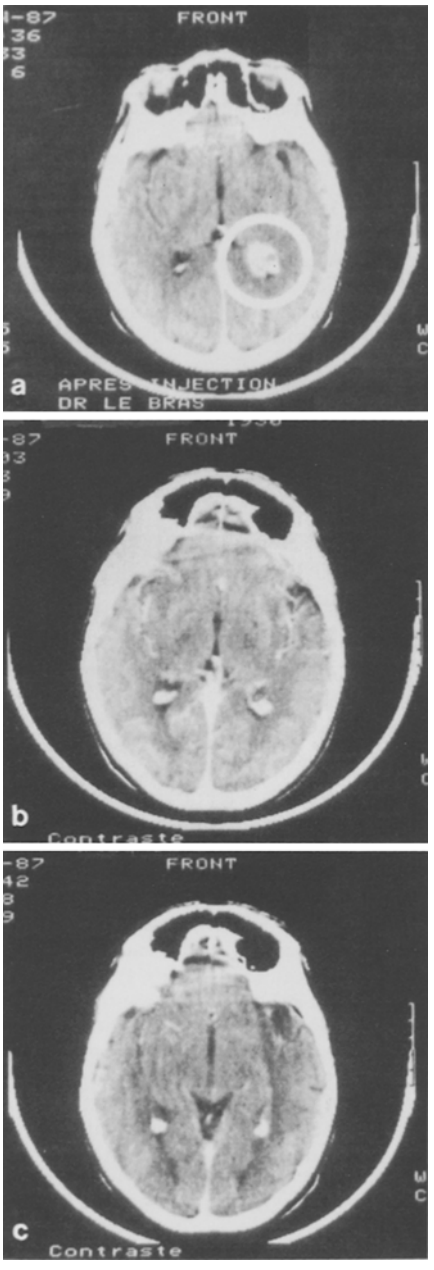

Fig. 2. Patient with three cutaneous metastases and one cerebral metastatic site, showing a complete response in non-visceral metastases and a partial response in brain metastases (duration of response, 26+ weeks)

Among the 42 patients entered, 3 were not evaluable (2 for prior irradiation of the target lesion and 1 for no clear evidence of metastases on a brain CT scan). The main characteristics of the 39 evaluable patients are presented in Table 1. There were 19 men and 20 women, with a median age of 49 years (range, 26–72 years) and a median Karnofsky performance status of 90% (range, 60%–100%). In all 16 patients (41%) showed cerebral metastases alone, whereas 23 patients (59%) also displayed visceral and/or non-visceral metastatic sites.

Cerebral metastases were multiple in 26 patients (66.7%) and single in 13 (33.3%). Among the 13 patients with a single cerebral metastasis, 5 were free of other metastatic sites and surgery could not be proposed. In all 16 patients (41%) had not undergone previous chemotherapy, whereas 18 had received one regimen and 5 had been given two or more polychemotherapeutic regimens (of which one contained a nitrosourea in 8 patients).

Table 3. Single vs multiple metastases

	Single	Multiple
Patients (*n*)	13	26
Responses:		
Complete	1	1
Partial	3	6
Median survival (weeks)	29	16
Range	8–146+	4–102+
6-month survival	64%	33%
1-year survival	22%	19%

Results

Clinical activity

Evaluation of cerebral lesions on CT scans showed 2 complete responses (CR), 9 partial responses (PR), 9 stabilisations (ST) and 19 cases of progressive disease (PD), leading to an overall response rate of 28.2%. Response was documented at the end of the induction therapy (8 weeks), except in two patients who responded at weeks 14 and 17, respectively. It should be noted that among the 11 responding patients, 7 with extra-cerebral metastatic sites presented a clinical response, especially a cutaneous CR. No patient achieved systemic response without a cerebral response. Among the 11 responding patients, clinical and functional improvement, in correlation with radiological response, was observed in 5. Characteristics of response are shown in Table 2 and illustrated in Figs. 1 and 2.

This response rate was significantly influenced by the prior chemotherapy, increasing to 50% in patients with no prior chemotherapy (16 patients) vs 13% among the 23 patients previously undergoing chemotherapy ($P < 0.01$). The median duration of response was 11 weeks (range, 8–102+ week) and overall median survival was 26 weeks (range, 4–146+ weeks), with 21% of patients still being alive after 1 year. Median survival in responders was 51 weeks (range, 11–102+ weeks) vs 15 weeks (range, 14–146+ weeks) in non-responding patients. The difference is highly significant ($P < 0.005$).

As described in Table 3, among the 13 patients presenting a single cerebral metastasis, 1 CR and 3 PRs were observed, whereas 1 CR and 6 PRs were noted among the 26 patients with multiple cerebral metastases. The median survival of patients with a single cerebral metastasis was 29 weeks (range, 8–146+ weeks), and 64% of these patients are still alive at 6 months. Patients with multiple cerebral metastases showed a median survival of 16 weeks (range, 4–102+ weeks), with 33% still being alive at 6 months. The 1-year survival was quite similar in both groups (22% for single vs 19% for multiple metastases). The

median survival of patients who had not previously undergone chemotherapy was double that of those previously treated (32 weeks vs 15.5 weeks).

Toxicity

Toxicity was mainly hematological, consisting of leucopenia and thrombopenia with the delayed characteristics typical of nitrosourea compounds (respective nadirs at days 42 and 36), and was never problematic. Gastro-intestinal toxicity was mild, with moderate to severe vomiting in only 43/153 administrations (28.1%). A transient increase in hepatic enzyme values (greater than grade I) was reported in two patients for (ASAT), nine patients for (ALAT) and one patient for alkaline phosphatases. No other major toxicity was reported.

Discussion

Malignant melanoma is the third most common cancer with cerebral metastases, after lung and breast cancer [16]. Despite a number of studies – especially in breast and small-cell lung cancer – reporting responses of cerebral metastases to chemotherapy alone [10, 13, 15], conventional therapy by combined modalities including chemotherapy is very disappointing; this may explain the large number of protocols and the lack of controlled studies. Moreover, comparison of results in different protocols is made difficult by the small number of patients, the lack of accuracy in evaluating the clinical activity and difficulty in calculating survival [9]. It is mainly admitted that median survival of patients treated with radiotherapy ranges between 3 and 6 months, with a 1-year survival of about 15%, whereas surgery – alone or combined with radiotherapy – achieves a median survival of 6 months [6, 17], with a 1-year survival of 20%–25%.

Our study shows that the nitrosourea fotemustine is active against cerebral metastases of malignant melanoma, with a significant ($P < 0.005$) increase in median survival between responding and non-responding patients. Our results are consistent with Retsas and Gershuny's [14] study on 100 patients presenting cerebral metastases of malignant melanoma; these authors obtained a response rate no greater than 10% (with a combination of polychemotherapy including CCNU and radiotherapy), but with a median survival that was significantly higher in responding patients than in non-responders [14]. Moreover, two factors influenced the response rate: the existence of a single metastatic lesion and the absence of previous chemotherapy; nevertheless, these two factors modify the percentage of 6-month survival but not of 1-year survival. Toxicity was, as expected, mainly hematological.

Due to the high response rate obtained in the present study especially in patients presenting a single metastasis and no prior chemotherapy, and the lack of major or uncontrollable toxicity, further studies of fotemustine – used in combination with either radiotherapy or other chemotherapeutic agents – are warranted.

References

1. Amer MH, Al-Sarraf M, Baker LH, Waitkevicius VK (1978) Malignant melanoma and central nervous system metastases: incidence, diagnosis, treatment and survival. Cancer 42: 660–668
2. Atkinson L (1978) Melanoma of the central nervous system. Aust NZ J Surg 48 (1): 14–16
3. Avril M-F, Bonneterre J, Delaunay M, Grosshans E, Fumoleau P, Israel L, Bugat R, Namer M, Cupissol D, Kerbrat P, Montcuquet P, Arcaute V, Bizzari J-P (1989) Combination chemotherapy of dacarbazine and fotemustine in disseminated malignant melanoma – experience of the French study group. American Society of Clinical Oncologists, San Francisco
4. Burke PJ, Mc Carthy WH, Milton GW (1971) Imidazole carboxamide therapy in advanced malignant melanoma. Cancer 27 (3): 744–750
5. Gottlieb JA, Frei E III, Luce JK (1972) An evaluation of the management of patients with cerebral metastases from malignant melanoma. Cancer 29 (3): 701–705
6. Hafstrom L, Jonsson PE, Stromblad LG (1980) Intracranial metastases of malignant melanoma treated by surgery. Cancer 46(9): 2088–2090
7. Jacquillat C, Khayat D, Banzet P, Weil M, Fumoleau P, Namer M, Avril MF, Lauvin R, Kerbrat P, Vilmer C, Bizzari JP (1988) Multicentric study of the nitrosourea fotemustine (S 10036) in advanced malignant melanoma (AMM) including patients with cerebral metastases. Neo-Adjuvant Chemother 169: 787–790
8. Jacquillat C, Khayat D, Avril MF, Banzet P, Weil M, Fumoleau P, Namer M, Lauvin R, Kerbrat P, Vilmer C, Bizzari JP (1989) Brain metastasis of malignant melanoma: clinical activity of the nitrosourea fotemustine (S 10036). Abstract, 13th congress of the ESMO, Lugano, 1988, Cancer Chemother Phormacol 23 [Suppl]
9. Katz HR (1981) The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. Int J Radiat Oncol Biol Phys 7 (7): 897–906
10. Kristjansen PEG, Hansen HH (1988) Brain metastases from small cell lung cancer treated with combination chemotherapy. Eur J Cancer Clin Oncol 24: 545
11. Kolaric K, Roth A (1980) Treatment of metastatic brain tumors with the combination of 1-methyl-1-nitrosourea (MNU) and cyclophosphamide. J Cancer Res Clin Oncol 97: 193–197
12. Posner JB (1977) Management of central nervous system metastases. Semin Oncol 4 (1): 81–91
13. Postmus PE, Haaxma-Reiche H, Sleijfer DTH, (1987) High-dose etoposide for central nervous system metastases of small cell lung cancer. Preliminary results. Eur J Resp dis 70 [Suppl 149]: 65
14. Retsas S, Gershuny AR (1988) Central nervous system involvement in malignant melanoma. Cancer 61 (9): 1926–1934
15. Rosner D, Nemoto T, Lane W (1986) Chemotherapy induces regression of brain metastases in breast carcinoma. Cancer 58: 832
16. Stridsklev IC, Hagen S, Klepp O (1984) Radiation therapy for brain metastases from malignant melanoma. Acta Radio Oncol 23 (4): 231–235
17. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF (1981) Intracerebral metastases in solid-tumor patients: natural history and results of treatment. Cancer 48 (2): 384–394

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