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Combination chemotherapy of dacarbazine and fotemustine in disseminated malignant melanoma

Experience of the french study group*

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Summary. A total of 70 patients presenting with a disseminated malignant melanoma were entered into a multicentric study of combination chemotherapy using dacarbazine and fotemustine. In all, 63 patients were evaluable, 31.8% of whom had previously received cytotoxic chemotherapy. The protocol consisted of induction treatment with a weekly infusion of 100 mg/m^2 fotemustine on days 1 and 8 and a daily infusion of 250 mg/m^2 dacarbazine on days 15/18 followed by a 4- to 5-week rest period. Responding and stabilized patients were given maintenance treatment comprising fotemustine (100 mg/m^2, day 1) and dacarbazine (250 mg/m^2, days 2/5) every 3 weeks. The response rate was 33.3% (9 complete responses (CRs) and 12 partial responses (PRs)) and was outstanding among pretreated patients (34.9%). Responses were also documented in cerebral (28.6%), visceral (23.1%) and nonvisceral (43.3%) metastatic sites. Toxicity was mainly hematologic (22.2%, grade III/IV leukopenia; 20.3%, grade III/IV thrombocytopenia) and was acceptable. These results are encouraging in terms of the antitumor activity against nonvisceral metastases (43.3%) and the percentage of CRs obtained (23.3%), and they confirm the activity of fotemustine in cerebral metastatic sites.

Introduction

Despite intensive use of polychemotherapeutic regimens, treatment of disseminated malignant melanoma remains very disappointing. The reference compound is currently dacarbazine, which achieves a reported 20.0%/25.0% response rate [2, 13, 14] with its main activity being observed in nonvisceral or visceral metastases and very little, if any, in cerebral metastases. We recently reported [11, 12] the confirmation of the activity of fotemustine, a new nitrosourea, against this disease obtaining a response rate of 24.2% (95% confidence interval, 17.4%/31.0%), with particularly strong activity being observed in brain metastases (25%). Moreover, therapeutic efficacy was increased among patients with no prior chemotherapy (30.7%). Since these two agents had shown no toxicologic potentialization, in May 1988 we initiated a multicentric study in an attempt to increase both the response rate and the median duration of response in patients with disseminated malignant melanoma.

Patients and methods

Patient selection

A total of 70 consecutive patients were entered in this study; 7 were not evaluable (due to protocol violation in 3 cases, nonmeasurable lesions in 2, an uncontrolled active infection in 1 patient and premature death in 1 case). Characteristics of the 63 evaluable patients included a sex ratio of 1.03 (32 men and 31 women), a median age of 40 years (range, 19/78 years), and a median Karnofsky performance status of 90% (range, 60%/100%). All patients had a histologically proven disseminated malignant melanoma; four patients showed ocular melanoma (6.3%) and three had mucous melanoma (1.8%). The primary tumor sites involved the head and neck (4.7%), arms (17.4%), legs (27%) and trunk (22.2%). In most cases, the Clark classification was grade IV/V (39.6%), and the Breslow value was >3.00 mm in 32.7% of patients. Prior treatment included: surgical treatment, 55 patients (87.3%); radiotherapy, 3 cases (4.8%) and chemotherapy, 20 patients (31.7%). The combination chemotherapy with fotemustine/dacarbazine was the first treatment ever received by 43 patients (68.3%). The dominant metastatic sites were cere-

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Table 1. Characteristics of response

Characteristic	Number of patients	Percentage
Response		
Complete	9	14.3%
Partial	12	19%
Minor	1	
Stabilization	12	
Progressive disease	29	
Response rate		33.3%
95% confidence interval		21.7%/44.9%
Metastatic site		
Cerebral (%)	2/ 7	28.6%
Visceral (%)	5/26	23.1%
Nonvisceral (%)	13/30	43.3%
Responses		
Untreated patients	15/43	34.9%
Treated patients	6/20	30%

Median duration of response: >19 weeks (range: >8/>34 weeks)

Table 2. Toxic effects of combination chemotherapy consisting of dacarbazine and fotemustine

Toxicity	Grade 0–I	Grade II–III	Grade IV
Leukopenia (%)	48.2	50	1.8
Thrombocytopenia (%)	62.9	25.9	9.2
Gastrointestinal toxicity (%):			
Fotemustine	63.2	36	0.7
Dacarbazine	47.6	52.4	-
ALAT (%)	91.3	8.7	-
ASAT (%)	90.9	4.5	4.5
Alkaline phosphatases (%)	100	-	-
Bilirubin (%)	100	-	-
Blood urea (%)	100	-	-
Creatinine (%)	100	-	-

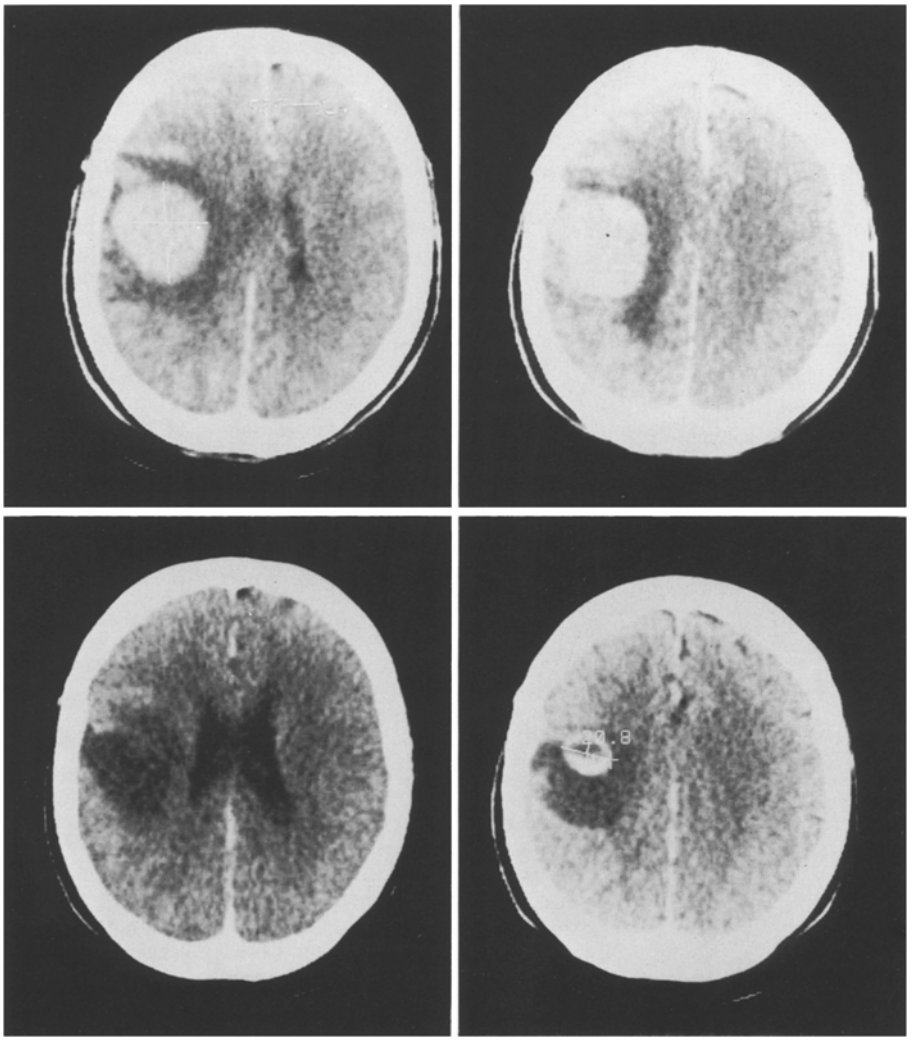

Fig. 1. a, b Partial response (PR) on cerebral metastatic site. Patient MOL., brain CT scan before treatment

Fig. 2. a, b Patient MOL., brain CT scan 8 weeks after treatment. Duration of response: 14 weeks

bral (7 patients; 11.1%), visceral (26 cases; 41.3%) and nonvisceral, including bone (30 patients; 47.6%).

Study design

The treatment protocol consisted of induction treatment for 8 weeks, including a weekly infusion of 100 mg/m^2 fotemustine on days 1 and 8 and a daily infusion of 250 mg/m^2 dacarbazine on days 15/18, followed by a 4- to 5-week rest period. Responding and/or stabilized patients were given maintenance treatment comprising fotemustine (100 mg/m^2, day 1) and dacarbazine (250 mg/m^2, days 2/5) every 3 weeks. Fotemustine and dacarbazine were given by intravenous 1-h infusion (protected from light) in a 250 cc solution (5% glucose for fotemustine, 9‰ saline solution for dacarbazine). Antitumor activity and toxicity were classified according to World Health Organization (WHO) criteria. Antitumor activity was based on and documented by objective clinical and/or radiologic (or echographic) responses and was analyzed during weeks 4/8 of the induction phase of treatment and then regularly during maintenance treatment of evolutive, measurable lesions. Evaluation of cerebral metastases was based on computerized tomographic (CT) brain scans.

Toxicity was thoroughly evaluated, being analyzed every week during induction treatment, then regularly before each infusion during maintenance treatment; biological tests included a blood cell count and determinations of blood urea nitrogen and serum creatinine levels, alkaline phosphatase values, total bilirubin levels and transaminase values (ASAT, ALAT).

Results

Antitumor activity

All patients were analyzed according to the protocol. Antitumor activity analysis performed at week 8 and during maintenance treatment is summarized in Table 1. We observed 9 complete responses (CRs), 12 partial responses (PRs), 1 minor response (MR), 12 stabilizations (ST) and 29 cases of progressive disease (PD), for an overall response rate (9 CRs +12 PRs) of 33.3% (21/63) (95% confidence interval, 21.7%/44.9%). Tumor lesions were regrouped according to dominant metastatic site and prognosis. Responses were also observed in cerebral (28.6%), visceral (23.1%), and nonvisceral metastatic sites (43.3%). A PR observed in a cerebral metastatic site is presented in Figure 1 (a and b). The median duration of response was >19 weeks (ranging from >8 to 34 weeks), but these results are underevaluated due to the lack of back-data, as 20 patients remain under treatment. The median duration of CRs, to date, is >24 weeks (range, >16 to >34 weeks). In the untreated patient group (43 cases), the response rate was 34.9% (7 CRs and 8 PRs) whereas it reached 30.0% among the 20 patients who had received prior chemotherapy. It is noteworthy that (a) none of the 3 patients who had previously received a nitrosourea showed an objective response and (b) among the 15 patients who had received prior dacarbazine chemotherapy, 2 showed a clinical response (13.3%).

Toxicity

The toxicity of this combination chemotherapy is presented in Table 2. It was mainly hematologic, consisting of leukopenia (22.2% grade III/IV) and thrombocytopenia (20.3% grade III/IV) which were delayed (respective nadirs on days 42 and 32); simultaneous grade IV toxicity of both types occurred in one patient (1.8%). Hepatic toxicity as evaluated by a transient increase in ASAT, ALAT values and was observed (ASAT: 13.6% greater than grade 0; ALAT: 26%). Gastrointestinal toxicity was mild (63.2% grade 0,I during fotemustine chemotherapy; 47.6% during dacarbazine treatment). No other major toxicity was reported.

Discussion

For the last 15 years, specific chemotherapy for metastatic malignant melanoma has scarely improved, despite the use of various polychemotherapeutic regimens that mostly contain dacarbazine since it represents the reference compound in this disease [2, 13, 14]. These combinations involved either bichemotherapy with a nitrosourea [4, 5] or with CDDP [8, 9] or a three-drug combination [1, 3, 6, 7, 10]. Global analysis comparing mono-polychemotherapeutic regimens does not seem to show a real difference in the average response rate or the median duration of response.

The activity of the new nitrosourea fotemustine, was recently reported in disseminated malignant melanoma with a response rate of 24.2% being noted in 153 evaluable patients, which reached 30.7% in previously untreated patients (62 cases) and with responses also being observed in cerebral (25.0%), visceral (19.8%), and nonvisceral (31.8%) metastatic sites [12]. Since no major antagonistic effect or synergic toxicity was reported, fotemustine was then tested in combination with the reference compound DTIC in an attempt to increase both the response rate and the duration of response. In the present study, the overall response rate was 33.3% among 63 evaluable patients, reaching 34.9% in untreated patients. These results confirm the clinical activity of both drugs and underline the efficacy of fotemustine chemotherapy in cerebral metastases [11]. Although combination chemotherapy did not appear to be more effective than single agent chemotherapy in visceral metastatic sites (23.1% for the combination, 19.8% for fotemustine alone, and 20%/22% for dacarbazine alone), the main impact of this combination was observed in nonvisceral metastatic sites (43.3% compared with 31.8% for fotemustine alone or 21.4% for DTIC alone) [3, 13]. Major toxicity was limited to leukopenia and thrombocytopenia, but both were easily controllable. In conclusion, this combination chemotherapy appears to be very promising for the treatment of patients with disseminated malignant melanoma, particularly in terms of the high response rate, the activity against cerebral metastases, and the low toxicity encountered.

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