Second-line chemotherapy of disseminated malignant melanoma with cystemustine at 60 mg/m^2: a phase II trial

Emilie Thivat[a,b], Xavier Durando[a], Michel D'Incan[c], Hervé Cure[a], Marie-Ange Mouret-Reynier[a], Jean-Claude Madelmont[b], Pierre Souteyrand[c] and Philippe Chollet[a,b]

Nitrosoureas possess some anti-tumor activity as a single agent in metastatic melanoma (MM). In a phase II trial, we evaluated the anti-tumor effects of cystemustine chemotherapy, a new nitrosourea, as a second-line treatment. Patients were required to have histologic evidence of disseminated MM and had failed in first-line chemotherapy. Treatment comprised cystemustine given at a dose of 60 mg/m^2 every 2 weeks by a 15-min infusion. From February 1997 to September 1999, 22 patients (median age 66 years) were enrolled and were assessable. Two complete responses, one partial response, three stable diseases and 16 progressions were observed, giving an overall response rate of 13.6%. Median duration of response was 10 months (range 4–63). Median survival of responders and non-responders was 11 and 4 months, respectively. However, hematological toxicity, particularly thrombopenia, was a limiting factor for one-third of patients. We conclude that cystemustine at 60 mg/m^2 is active in patients who progressed after one line of chemotherapy in advanced disease, and offers the possibility of complete responses and long durations of these responses. *Anti-Cancer Drugs* **16:1003–1007**

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[a]Unité d'Oncologie Appliquée, Centre Jean Perrin, Centre Hospitalier et Universitaire, Clermont-Ferrand, France, [b]UMR 484 INSERM, Université d'Auvergne, Clermont-Ferrand, France and [c]Service de Dermatologie, Hotel-Dieu/Polyclinique, Centre Hospitalier Régional et Universitaire de Clermont-Ferrand, Clermont-Ferrand, France.

Correspondence to E. Thivat, Unité d'Oncologie Appliquée, Centre Jean Perrin, 58 Rue Montalembert, BP 392, 63011 Clermont-Ferrand Cedex 1, France.
Tel: +33 4 73 27 80 05; fax: +33 4 73 27 80 29;
e-mail: Recherche.CLINIQUE@cjp.fr

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Introduction

Cutaneous melanoma represents only 2% of malignant tumors, but its incidence is rapidly increasing in the Caucasian population. Metastatic melanoma (MM) patients have a poor prognosis with median survival time of around 6–7.5 months [1] and limited responsiveness to mono- or poly-chemotherapy, or current immunotherapy regimens. Only a few drugs [chloronitrosoureas (CENUs), dacarbazine (DTIC), platinum analogs, vinca alkaloids or taxanes] have produced consistent responses, with an objective response rate of 10–25% [1–3] in first-line treatment.

Nevertheless, a large population of patients with disseminated MM fails first-line therapy, but could benefit from a second treatment regimen. The place of chemotherapy in such patients is unclear [4] since only a few studies have focused on second-line treatment [5–10].

Cystemustine, a third-generation CENU developed in our institution, is mostly active against glioma and melanoma [11]. In two phase II trials conducted by the EORTC Clinical Studies Group [12,13], with cystemustine at 60 and 90 mg/m^2 as a first- or second-line treatment, 25 and 54 patients, respectively, were enrolled. We have reported overall response rates (ORs) of 9 and 11%, respectively; 10 of 25 and 21 of 54 had previously been treated with other chemo- and/or immunotherapy. A dose-limiting toxicity meant that a dose reduction to 60 mg/m^2 after the third cycle for all the patients treated with an initial dose of the 90 mg/m^2 had to be adopted. However, in these studies, cystemustine ORs have been evaluated on a heterogeneous population (first- and second-line treatment).

In the current study, this trial focused on the administration of 60 mg/m^2 cystemustine as second-line treatment to 22 patients with disseminated MM.

Materials and methods

Patients

In order to be enrolled in the study, all patients were required to have histologic evidence of disseminated MM. Eligibility criteria included at least one measurable cutaneous or visceral metastatic lesion not previously irradiated, a WHO performance status of 0–2, normal white blood cell count (> 4000/μl) and platelet count

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($>100\,000/\mu l$), and a normal renal and liver function. In addition, patients must have received only one prior line of chemotherapy except for choroid melanoma, for which no previous chemotherapy was accepted. The study protocol was approved by local ethical committees and all patients provided written consent for the trial.

Treatment schedule

Cystemustine was administered i.v. at $60\,mg/m^2$, being infused for 15 min in 100 ml of 5% dextrose. The treatment plan consisted of one administration every 2 weeks after verification of the blood parameters. For granulocyte count $<1500/\mu l$ or platelet count $<100\,000/\mu l$ on day 14, patients would be untreated with a new cycle and injection might be delayed for a minimum of 2 weeks. However, a delay >4 weeks between 2 cycles led to premature treatment being discontinued. Treatment was continued until progression or unacceptable toxicity occurred, with a maximum of 6 cycles. Each patient had to receive at least 2 cycles of treatment to be assessed.

Response assessments

Disease response was assessed by computed tomography scans or magnetic resonance imaging after cycles 2, 4 and 6, and then every 2 months. To qualify as a confirmed response, two objective assessments of status at least 4 weeks apart were required.

Responses were recorded using WHO criteria [14] and defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The OR was defined as the percentage of patients with confirmed CR or PR.

Statistical analysis

Duration of response (responder patients: PR + CR) and overall time to progression were measured from initiation of cystemustine chemotherapy to the first observation of PD. Survival was calculated from the start data of chemotherapy until death or last observation. Patients who had not progressed or were known to be alive at the time of analysis should be censored at the time of the last follow-up. Median survival and median duration of responses were estimated by the Kaplan–Meier method. The survival curves were compared using log-rank tests.

Results

The patient characteristics are given in Table 1. Twenty-two patients with disseminated disease were included. Twelve patients were male and 10 patients were female. Three of them had melanoma of the choroid, whereas all the others had primary cutaneous melanoma. Previous treatment were DTIC (10 patients) or fotemustine (one patient), polychemotherapy (four patients), interferon (IFN) (one patient) and combined biochemotherapy (IFN and chemotherapy) (three patients).

Table 1 Patient characteristics

Characteristics	*n*
Total	22
Included patients	22
Eligible patients	22
Fully evaluable patients	22
Sex	
male	12
female	10
Median age [years (range)]	63 (17–76)
WHO performance status	
0	10
1	7
2	5
Primitive tumor sites	
limbs	10
choroid	3
others	3
missing	6
Metastatic sites	
bone	1
liver	6
lymph node, skin	13
lung, pleura	10
Central nervous system (CNS)	5
other	6
Previous treatments	
monotherapy/DTIC	10
monotherapy/fotemustine	1
polychemotherapy	4
IFN-α	1
IFN + chemotherapy	3
No previous treatment (ocular melanomas)	3
Prior surgery	18
Prior radiotherapy	7

The median number of courses of cystemustine was 3 ± 2 cycles and eight out of the 22 patients received at least 6 cycles. The main reason for stopping treatment before 6 cycles had been completed was disease progression. However, seven patients stopped treatment because of toxicity and among them five received only 3 cycles.

Results of cystemustine treatment are described in Tables 2 and 3. All patients included were evaluated for response and toxicity. OR was 13.6% [95% confidence interval (CI) 3–35%] with two CRs, one PR and three SDs (Table 2). For one patient presenting with CR previously relating to pulmonary metastases, CR was obtained after 2 courses and continues after 63 months. For the second one presenting with CR with metastases (local/regional) at inclusion, he achieved a remission after 7 courses, remained in CR for 10 months after treatment and then started to relapse. He died 1 month later due to disease progression. The patient presenting with a PR had cutaneous metastases and lymph node involvement, PR was obtained after 2 courses and persisted for 4 months after treatment started. This patient died 2 weeks after clinical disease progression.

The median duration of response was 10 months (range 4–63) and overall time to progression was 1 month (range 0–63) (Table 3). Considering all the patients, the median survival was 4 months (Fig. 1). The median survival of

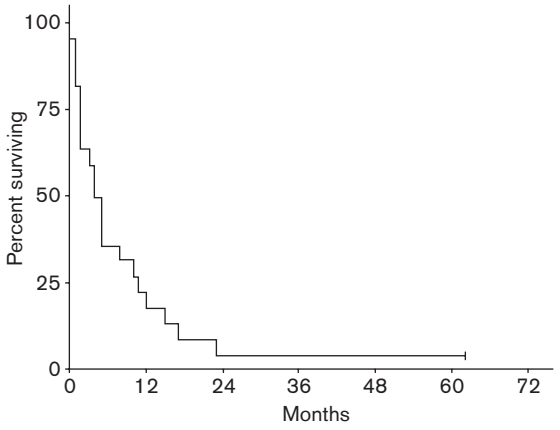
Table 2 Responses to cystemustine treatment

Response	*n* (%)
Eligible patients	22 (100)
CR	2 (9.1)
PR	1 (4.5)
SD	3 (13.6)
PD	16 (72.7)

Table 3 Time to progression and survival data from the start of cystemustine treatment

	Median (range)
Median response duration (months)	10 (4–63)
Median time to progression (months)	1 (0–10)
Median overall survival (months)	4 (0–63)
Responders (CR + PR)	11 (4.5–63)
Non-responders (SD + PD)	4 (0–23)
SD	8 (5–15)
PD	2 (0–23)

Fig. 1

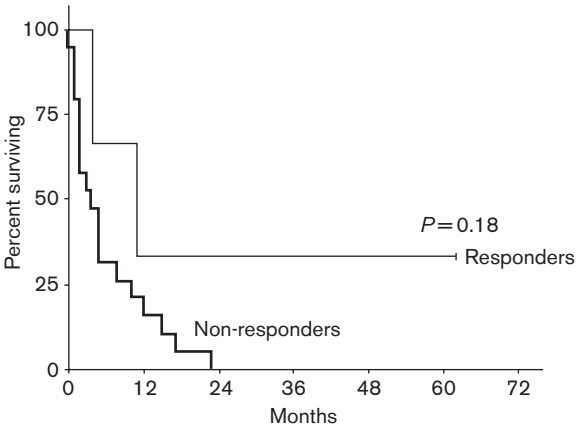


Kaplan–Meier plot of survival after the start of cystemustine monotherapy.

responders and non-responders was 11 and 4 months, respectively ($P = 0.18$) (Fig. 2).

Toxicity data is given in Table 4. The major problems were hematological toxicity (without bleeding), and consisted of thrombocytopenia (WHO grade 3 in 22.7% of patients and grade 4 in 18.2%) and neutropenia (WHO grade 3 in 18.2% of patients and grade 4 in 4.5%), and were mainly responsible for early treatment being discontinued. Nevertheless, only two cases of febrile aplasia were observed (9%). The main non-hematological toxicity was nausea and vomiting, only grade 3, in 9% of patients.

Fig. 2



Kaplan–Meier plots of survival after the start of cystemustine monotherapy in responders and non-responders.

Table 4 Maximum toxicity observed per patient

	WHO grade			
	1	2	3	4
Hematological toxicity [% (*N*)]				
anemia	10 (2)	20 (4)	10 (2)	0 (0)
leukocytes	18.2 (4)	18.2 (4)	13.6 (3)	0 (0)
neutrophils	4.5 (1)	13.6 (3)	18.2 (4)	4.5 (1)
thrombocytes	18.2 (4)	4.5 (1)	22.7 (5)	18.2 (4)
Non-hematological toxicity [% (*N*)]				
nausea/vomiting	4.5 (1)	18.2 (3)	0 (0)	0 (0)
alopecia	0 (0)	0 (0)	0 (0)	0 (0)
febrile aplasia	0 (0)	4.5 (1)	4.5 (1)	0 (0)

Discussion

The nitrosourea family possesses some anti-tumor activity as a single agent in MM, with an OR from 9 to 22% [3], but the standard chemotherapy remains DTIC. Recently, Avril *et al.* [15] showed that fotemustine treatment is associated with a significant improvement in the best OR compared with standard treatment, DTIC, as first-line treatment in MM [15]. This study confirms the activity of nitrosourea as a single agent in first-line treatment and shows that it could become the standard mono-chemotherapeutic regimen.

Our study aimed at evaluating the activity of single-agent cystemustine at 60 mg/m^2 every 2 weeks in disseminated MM only as second-line treatment. In the current study, the cystemustine OR (13.6%) was close to that observed in our two previous trials (11.3 and 9%), inspite of different dosages (90 and 60 mg/m^2, respectively) and the fact that the cystemustine response rate was evaluated on overall patients treated in first and second line, and not separately [12,13].

Moreover, the OR of cystemustine of 13.6% (95% CI 3–35%) is comparable with other single treatments against previously treated MM. Only a few trials of monotherapy (treosulfan, vindesine, vinorelbine tartrate, paclitaxel and fotemustine) used as second-line treatment for melanoma have been published and related to a response ranging from 0 to 20% [5–8,16]).

In addition, we have reported two patients showing long-duration CRs [10 months for one and over 5 years for the other (still in CR)], as well as one PR (4 months). Interestingly, the median response duration of 10 months (mean 26 months) is particularly high with cystemustine treatment compared with first-line DITC or fotemustine treatment, which generally varies from 4 to 7 months [1,15,16]. Some reports have already described long-term survival (several years) in patients with MM treated with chemotherapy. Most of these results, conversely to our cases, were obtained for patients treated by chemotherapy association. In a phase III study, eight patients with CRs who survived 6 years after the treatment were reported from 580 patients treated by DTIC alone or in association with carmustine, lomustine, vincristine or a hydroxyurea [17]. Petit *et al.* [18] reported five of 160 patients presenting with long-term remission 7 years after fotemustine chemotherapy followed by surgery.

Moreover, reports of CRs are rare in MM. The percentage of CRs with DTIC in first-line treatment was lower than in the fotemustine (5% or below) [15]. In our study with cystemustine as second-line treatment, the percentage of CRs [9.1% (two of 22)] is particularly important and seems to be an interesting point of this treatment which might be confirmed in a largest trial.

Median overall survival after the beginning of cystemustine chemotherapy was 4 months, with a median survival of responder patients of 11 months. These survival times are in good agreement with the median survival times after second-line monotherapy of 4–6.5 months reported in the literature [5–7].

We have already shown in the two previous trials [12,13] that drug toxicity was mainly hematologic, especially on platelets, and was sometimes dose limiting. WHO grade 3/4 toxicity for platelets observed in 41% of the present patients appeared unexpectedly frequent compared with the prior trial using 60 mg/m^2 (5%) [12]. It was comparable with the trial testing 90 mg/m^2 (43%) [13] for which a dose-limiting toxicity had meant a reduced dose of 60 mg/m^2 had to be used after the third cycle. However, no life-threatening side-effects were registered.

Numerous approaches, e.g. polychemotherapy and biochemotherapy, have already been tested to enhance the therapeutic index of nitrosoureas [1,2]. These had an increased response rate without a significant improvement in overall survival, few durable CRs and were often associated with increased toxicity. Recent studies suggest the potentiation of anti-tumor activity by methionine deprivation [19–23]. Methionine restriction, known to inhibit the growth of human and animal tumors (*in vitro* and *in vivo*) [19], used in association with cytostatic drugs (fluoropyrimidines, nitrosoureas, platinoids) produced a substantial improvement in the therapeutic index [20–22] by reducing chemoresistance mechanisms [23]. The potentiating effect of methionine depletion on cystemustine treatment has been shown on B16 melanoma-bearing mice [24]. On the basis of this experimental data, we initiated a phase I clinical trial of dietary methionine restriction in association with cystemustine treatment for MM [25].

In conclusion, cystemustine given at 60 mg/m^2 every 2 weeks is active in previously treated MM and the response rate remains comparable to those obtained with other single agents used as second-line treatment. The CR rates as well as the duration of these responses are valuable results for a treatment administered in monotherapy.

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