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Fotemustine with or without Dacarbazine for Brain Metastases of Malignant Melanoma

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FOTEMUSTINE (Laboratoires Servier, Belgium) is a new nitrosourea which is active against cerebral metastases of melanoma due to its ability to cross the blood–brain barrier, and also against visceral and non-visceral metastases. We present our experience using fotemustine, with or without dacarbazine, in patients with brain metastases of melanoma [1].

18 patients with histologically confirmed malignant melanoma and radiologically detected brain involvement were included, provided that consciousness and mentality were preserved.

Their age range was 19–75 years (median 45.5), Karnofsky performance status was higher or equal to 60% and life expectancy was at least 3 months.

The primary site was skin in 16 patients, rectum in 1 and eye in 1. Previous treatments for brain metastases included craniotomy followed by radiotherapy (30 Gy) in 4, and radiotherapy only (30 Gy) in 2 patients. Steroids were administered in all the patients, starting at least 8 days prior to the protocol. Previous systemic treatment was immunotherapy with or without dacarbazine in 7 patients.

Treatment protocols included three versions, according to the different phase II trials with fotemustine alone or fotemustine–dacarbazine combinations.

The first version consisted of a 7-week induction of fotemustine 100 mg/m^2 on days 1, 8 and 15, then 4 weeks' rest. If response or stabilisation was documented on evaluation, maintenance with fotemustine 100 mg/m^2 every 3 weeks was given until progression was observed. Follow-up intervals were of 6 weeks.

The second version consisted of a 7-week induction of fotemustine 100 mg/m^2 on days 1 and 8, and dacarbazine 500 mg/m^2 on days 15 and 16. If response or stabilisation was documented on evaluation on days 49 or 50, 6-week maintenance courses of fotemustine 100 mg/m^2 on day 1 and dacarbazine 500 mg/m^2 on days 2 and 3 were given, until failure was observed. Follow-up intervals were of 6 weeks.

The third version consisted of dacarbazine 400 mg/m^2, followed 4 hours later by fotemustine 100 mg/m^2. Maintenance courses were to be administered to the non-progressor patients, 28 days later, including dacarbazine 250 mg/m^2 followed 4 hours later by fotemustine 100 mg/m^2 on days 1 and 8.

The overall response rate (CR + PR) of brain metastases to these treatments was 22%, for a median duration of 4 months. 3 patients were treated according to the first version, of whom 1 achieved a CR for 3 months, and one SD for 1 month. 13 patients were treated according to the second protocol, of whom 3 achieved PR for a median duration of 4.5 months, 1 MR for 8 months and 1 SD for 4.5 months. 2 patients were treated with the third version, and no response was observed.

All the responders had a primary cutaneous melanoma. No response was found in meningeal spread. Median survival of brain responders was 7.5 months, and that of the non-responders was 3 months (not statistically significant).

Toxicity was generally mild. Grade I-II thrombocytopenia was observed in 46% and grade I-II nausea and vomiting in 61% of the patients. A transient increase in serum transaminase level was noted in 23% of patients.

The response rate achieved in the brain is attributed to the efficacy of fotemustine, since this drug is known to cross the blood–brain barrier [2] and dacarbazine to a much lesser extent; and spontaneous regression of metastatic melanoma occurs only rarely [3]. Dacarbazine failed to enhance the efficacy of fotemustine against cerebral metastases [4]. None of the patients in our series had been previously exposed to nitrosourea, but 83% of the patients who had been previously treated by immunotherapy and dacarbazine for systemic metastases failed to respond to fotemustine.

The first treatment version was also used by Jacquillat *et al.* who reported a response rate of 28% (CR 5%; PR 23%) in 39 patients with brain metastases [2].

The response rate achieved by the second treatment version was 23%. No comparable literature data are available.

The third version has been reported to yield an extracerebral response rate of 35%, but a cerebral response rate of 0% [5].

We conclude that treatment based on fotemustine was associated with clinical and radiological evidence of regression of brain metastases of malignant melanoma reflecting the intracerebral activity of the drug. Our results confirm other investigators' observations.

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