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Letter to the Editor

Effect of DDMP (2, 4-Diamino-5-3′, 4′-Dichlorophenyl-6-Methylpyrimidine) on Brain Gliomas—A Phase II Study*

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DESPITE favorable results observed in the treatment of brain gliomas with nitrosourea derivatives [1–4] and procarbazine [4], the role of chemotherapy in the treatment of these neoplasms remains modest. There is, therefore, an urgent need for new active agents, which could be used either alone or in combination with the previously mentioned drugs.

DDMP was chosen for this trial because it readily crosses the blood–brain barrier and because its peripheral side effects may be prevented by the administration of cytrovorum factor, which poorly crosses that barrier.

Twenty-nine patients, 24 males and 5 females, with symptoms and signs of recurring primary brain gliomas entered the study between September 1978 and August 1979. All patients underwent neurosurgery at least 3 months prior to their entry into the study, and all except two had radiotherapy completed at least 2.5 months prior to the beginning of the DDMP trial. Four patients were previously treated by chemotherapy; three had received CCNU and one VM-26 plus CCNU. Two of them had responded to the treatment. Five other patients had received mizomidazole, a radiosensitizer, during radiotherapy.

The pathological distribution of the tumors was as follows: 16 glioma multiforme, 9 astrocytoma grade III–IV, 3 astrocytoma grade I–II, and 1 spongioblastoma polare. The median age was 50 years (range 28–63). The median Karnowsky index was 62 (30–80). All patients had normal hematological, renal and liver functions when entering the study.

The scheduled dose of DDMP was 75 mg per m^2 of body surface once a week, repeated five times. The citrovorum factor was given orally at 10 mg per m^2 concomitantly to DDMP administration. The total doses of DDMP actually given are summarized in Table 1.

Table 1. Total doses of DDMP actually administered

Doses of DDMP (mg)	Number of patients
250–600	8
625	10
675–1500	11

The effect of DDMP was evaluated by the rate and the length of objective remission defined as clear-cut improvement of at least one neurological sign persisting 6 weeks or more after a complete discontinuation of corticosteroid administration. Such an objective remission was observed only in one patient.

The first patient who presented an objective remission, a 39-year-old man, was operated for a left frontal astrocytoma grade III–IV and received cranial irradiation. He then received an adjuvant chemotherapy combining VM-26 and CCNU. After 2 years tumor recurrence was observed; right-side weakness and aphasia become more conspicuous and intracranial hypertension developed. He received dexamethazone 10 mg per m^2 and two cures of DDMP 150 mg per week × 5. The neurological examination returned to what it was during the post-operative 2-year period, and the patient remained improved for another year and a half, but his brain CT-scan remained unchanged. The patient died from an acute monocytic leukemia.

The second objective remission was observed in a 46-year-old man who underwent a partial resection of a right frontal glioma

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multiforme infiltrating the corpus callosum and the thalamus. The operation was followed by a 6000 rad irradiation. No chemotherapy was given until the recurrence of neurological signs. A year and a half after neurosurgery, he complained of headaches, and mental disturbances were noted. He then received 5 mg of dexamethazone daily for 3 weeks and had 8 weekly administrations of DDMP (100–150 mg). The clinical improvement persisted for $3\frac{1}{2}$ months.

In nine other patients, there was also some clinical improvement but it did not persist long enough after the discontinuation of steroids to be considered as objective remission. These short remissions were attributed mainly, if not exclusively, to dexamethazone.

CCNU. This case will be reported in detail. Other side effects, especially digestive symptoms, were rare and usually not severe.

In conclusion, the efficacy of DDMP, given alone according to the schedule used in this trial, appears very modest in the treatment of recurrent brain gliomas. The observed response rate is 7%, and there is an 95% chance that it will not exceed 16%. Of course, our criteria for objective remission are rather rigid and short-lasting tumour regressions could have been overlooked. Such possible short remissions are of no interest if DDMP is used alone, but may be an indication for combining the drug with other anticancer agents.

The toxicity observed in this study was

Table 2. Side effects observed during DDMP-administration

Side effects	Mild	Moderate	Severe
Nausea/vomiting	1	5	—
Anorexia	2	2	—
Diarrhea	—	—	1
Infection	2	1	1
Skin rash	2	1	1
Mucositis	—	1	—
Headache	—	2	1
Depression	1	1	1
Alopecia	—	1	—
Asthesia	1	—	—
Epistaxis	—	—	1
Fever	—	1	—
Disorientation	—	1	—
Hematologic			
WBC	$(4.5 \times 10^3 – 3 \times 10^3)$	$(3 \times 10^3 – 2 \times 10^3)$	(2×10^3)
	4	6	1
Platelets	$(150 \times 10^3 – 70 \times 10^3)$	$(70 \times 10^3 – 40 \times 10^3)$	(40×10^3)
	3	3	5

The most common type of toxicity was a decrease in WBC or/and platelet counts, observed in 11 patients (Table 2). In those patients DDMP administration had to be delayed or stopped but in all cases the hematological abnormalities were reversible. The acute monocytic leukemia responsible for the death of one of the two patients who responded to DDMP was attributed to chemotherapy, which also included VM-26 and mild. The reasons for this good tolerance could be the absence of previous chemotherapy in 25 of the patients, of irradiation of sites other than the cranium, and of bone marrow metastases in patients with brain gliomas. In addition, the median age of our patients was relatively low. Therefore, a possibility remains that higher doses of DDMP could be used in patients with brain gliomas to improve the results obtained in this study.

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