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Recurrent Medulloblastoma

Lack of Response to High-Dose Methotrexate

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Medulloblastoma accounts for approximately 20% of primary intracerebral tumours in children and the 5-year survival is still in the region of 40% [1, 5]. Several studies have shown that recurrent medulloblastoma sometimes responds to chemotherapy; the drugs most widely used are nitrosoureas, procarbazine and vincristine, alone or in combination. Unfortunately, the response rates are low and responses are not usually sustained even using these agents in combination [3, 4, 7]. Information on responsiveness to other drugs is, therefore, urgently needed.

Rosen et al. [6] reported responses in five of seven children treated with high-dose methotrexate (HD MTX) for recurrent medulloblastoma, and Djerassi [2] also reported a response in one case. HD MTX/folinic acid (FA) therapy is non-myelosuppressive and, consequently, is attractive as a candidate for adjuvant use in newly diagnosed patients. We have, therefore, attempted to conform the anti-tumour activity in five children with recurrent medulloblastoma.

Five patients with recurrent medulloblastoma were treated. In each the initial diagnosis had been made by biopsy at the time of presentation. Details of the cases are given in Table 1. Each had been treated initially by craniospinal irradiation (50 Gy to the posterior fossa, 35 Gy to the whole brain and 30 Gy to the spinal cord). The recurrence in one patient (case 1) had been treated, before HD MTX, with six injections of vincristine, followed by three courses of procarbazine. The other patients had not received chemotherapy at any stage. One patient (case 4) had received further irradiation for a previous relapse.

Recurrence was diagnosed by unequivocal clinical deterioration accompanied by evidence from CT scan, lumbar puncture or bone-marrow examination and bone X-rays. The interval between the primary treatment and the start of the methotrexate infusions (after recurrence) ranged from 6 months to 5½ years.

Methotrexate was administered as a 24-h infusion at a dose of 2.5 g/m^2 with hydration using N/5 dextrose-saline. Urine alkalisation was not used. At 30 h, 12 mg of folinic acid (FA) was given and repeated every 6 h for 72 h. Serum MTX levels were measured in all five patients by radio-immunoassay at 6, 24, and 48 h; in three patients lumbar CSF levels were measured at 6 h and, in one instance, also at 24 and 48 h. The 6-h levels were measured for comparison with Rosen's data. Full blood counts, blood urea and electrolytes, serum creatinine and liver function tests were monitored before and after each course. The MTX infusion was repeated every 3 weeks as long as the haematological and biochemical parameters were normal and there was no disease progression. We

Table 1. Clinical details of the patients

Case	Age at relapse (years)	Sex	Steroids	Performance status (Karnovsky)	Disease-free interval	Site of recurrence	No. of infusions	Response
1	11	M	0	30	3 years	4th ventricle	1	Rapid progression
2	2½	M	Dexamethasone 6 mg od	30	6 months	Meninges	2	Progression
3	17	M	0	60	2 years	4th ventricle	5	Slow progression
4	11	M	0	80	5½ years	Base of brain, nasal cavity, maxillary sinus	2 2	Slow progression
5	14	M	0	80	3 years	Meninges, widespread bone and marrow disease	2	Slow progression

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Table 2. Blood and CSF levels of MTX at varying times after the start of treatment. Data are taken from the paper by Rosen et al. [9] and the present study

Time (h)	Blood		CSF	
	Rosen	Present study	Rosen	Present study
4	2×10^{-3} M		7×10^{-6} M	
6		2×10^{-5} M		5×10^{-6} M
12	4×10^{-5} M		3×10^{-5} M	
24	4×10^{-6} M	2×10^{-5} M	5×10^{-6} M	1×10^{-6} M
48	3×10^{-7} M			

defined an 'adequate trial' as the completion of two courses of HD MTX/folinic acid.

We did not observe a single response in these five patients. Patient 1 had progressive disease after one course and died 3 weeks later; by our arbitrary definition, this patient is not 'eligible' for assessment of response. Each of the remaining patients completed at least two courses of MTX/folinic acid. Patient 2 showed transient clinical improvement after the first course, but after the second he deteriorated rapidly and died. The third patient improved a little clinically after three courses of MTX, but the CT scan did not confirm a response and he deteriorated after two further courses. Patient 4 had massive recurrence extending into the nasal cavity, which grew steadily during two courses. The fifth patient had widespread skeletal metastases and extensive marrow infiltration; there was no clinical response to a course of MTX and a further marrow biopsy showed the infiltration by tumour to be unchanged.

The treatment was well tolerated. There were no instances of significant blood-count depression. Mild nausea was frequent but there was no vomiting. One patient developed oral mucositis, mild abdominal pain and diarrhoea, all symptoms settling rapidly and spontaneously.

The blood and CSF levels are shown in Table 2 and compared with the data of Rosen et al. [6]. All patients had 6- and 24-h serum levels in excess of 1×10^{-5} M. At 48 h the levels were more scattered, ranging from 2.1×10^{-6} M to 1.7×10^{-7} M. The 6-h CSF levels were more variable than the blood levels and ranged from 1×10^{-6} M to 1.8×10^{-5}. The 24-h level (Patient 1) was 1×10^{-6} M and the 48-h level was 2.2×10^{-7} M.

We have not confirmed the favourable results reported by Rosen et al. [6] and Djerassi [2]. The schedules of MTX administration were, however, different. Rosen et al. [6], for instance, treated their patients with a 3–5-fold higher dose per course than we used: peak serum concentrations were, therefore, up to 2 logs higher and CSF concentrations slightly higher in Rosen's patients than in ours. Three-weekly, rather than two-weekly, administration of MTX might have reduced its efficacy in our study; to counter the effect of the longer interval between courses, we decided to use a 24-h infusion of MTX, prior to folinic acid rescue, in order to expose as many actively cycling medulloblasts (tumour cells) as possible to the S-inhibitory effects of this agent. This delay in 'rescue' resulted in comparable 'areas under the curve' of serum and CSF MTX concentrations in our patients and Rosen's. Intrinsic resistance to MTX, rather than lack of drug access because of any putative blood/brain tumour barrier, is suggested by failure of response of metastatic disease vascularised via the systemic circulation in two patients (Case 4 and 5), neither of whom had received prior chemotherapy.

The International Society of Paediatric Oncology ("SIOP") is planning a study on newly diagnosed patients with medulloblastoma, of adjuvant HD MTX/folinic acid after surgery and before radiation therapy. The proposed dosage of MTX is similar to that used in our study. We would suggest, in view of the results reported here, that further data on optimal dosage and scheduling of MTX/folinic acid is needed before this large and important multi-centre study opens for patient entry.

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