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Journal
The Journal of Pediatrics, 113(3)

ISSN
0022-3476

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Publication Date
1988-09-01

DOI
10.1016/s0022-3476(88)80662-0

Salvage chemotherapy for recurrent primary brain tumors in children

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Sixty consecutive evaluable children with recurrent primary tumors of the central nervous system were treated with a regimen of vincristine, nitrogen mustard, procarbazine, and prednisone over a 12-year period. Tumor types included medulloblastoma (19), brain-stem glioma (16), astrocytoma (13), and a miscellaneous glioma (12). Responses and sustained survivals were achieved. Responses were highly dependent on tumor type. Disease progression was halted in 73% of the children with medulloblastoma, and three have survived in complete remission for more than 10 years from the start of therapy with vincristine, nitrogen mustard, procarbazine, and prednisone. Two of four patients with anaplastic glioma, are long-term survivors. In contrast, less than one third of children with brain-stem gliomas responded. Toxicity consisted mainly of neutropenia, thrombocytopenia, infections, and rarely a procarbazine rash. (J PEDIATR 1988;113:601-6)

Therapy for recurrent brain tumors in children remains unsatisfactory; most die of their disease regardless of therapy.[1] We have reported on the responsiveness of recurrent brain tumors in children to chemotherapy with vincristine, nitrogen mustard, procarbazine, and prednisone.[2] A later prospective randomized trial confirmed the contribution of nitrogen mustard, although because of the greater toxicity, no difference in survival was observed between the two treatment regimens.[3] Since then we have extended the use of MOPP to primary therapy for infants with brain tumors in whom radiotherapy may result in devastating sequelae.[4] The efficacy of MOPP as primary therapy for infants with medulloblastomas after surgery has been established.[5]

We now report on our experience of more than 10 years with MOPP as salvage therapy for recurrent brain tumors in children. Our experience allows assessment of the comparative responsiveness of different tumor types and shows the durability of the response in some children with medulloblastoma. A preliminary report has appeared.[6]

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METHODS

Patients. Sixty-five children with a median age of 6 years (range, 1 to 16 years) were treated with MOPP for recurrent brain tumors. Sixty patients were eligible for evaluation; the other five patients were excluded because 1 died before completion of the first MOPP course, the records of two others were not available, and two patients received intrathecal methotrexate concurrently with MOPP. All patients had failed to respond to primary therapy consisting of either surgery, radiation, or both. Thirteen patients had also failed to respond to a previous chemotherapy regimen for tumor recurrence. Previous chemotherapy consisted of one or more of the following drugs: vincristine, lomustine, methotrexate (systemic, intrathecal, or both), etoposide, and cisplatin.

CT	Computed tomography
MOPP	Nitrogen mustard, vincristine, procarbazine and prednisone

The distribution of tumor types and patients' ages and gender are listed in Table I. Tissue diagnoses were available for all patients with medulloblastomas but for only 5 of 16 of those with brain-stem gliomas. Among the group

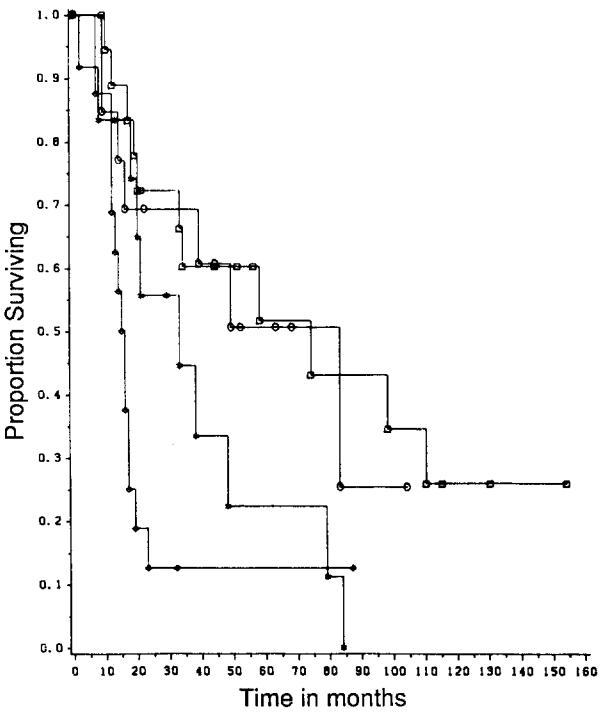

Fig. 1. Meier-Kaplan curve for survival from the time of diagnosis in patients with medulloblastomas *(square)*, gliomas *(circle)*, brain-stem gliomas *(diamond)*, and miscellaneous tumors *(star)*.

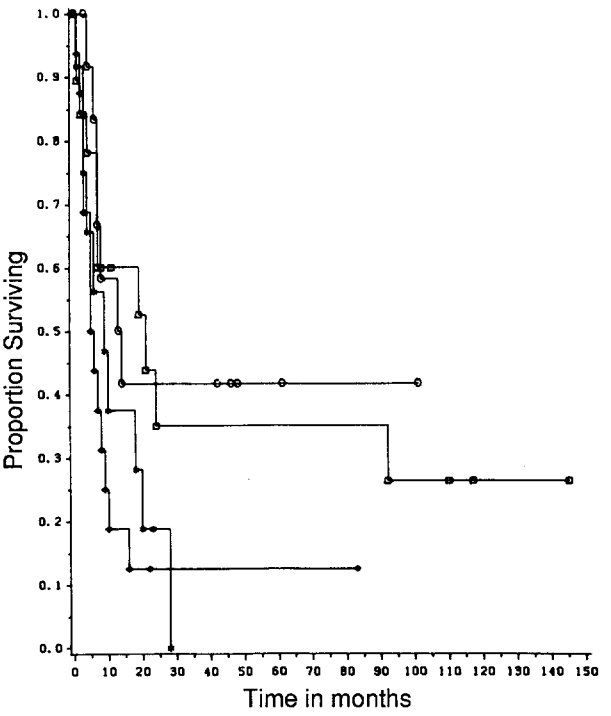

Fig. 2. Meier-Kaplan curve for survival from initiation of MOPP therapy in patients with medulloblastomas *(square)*, gliomas *(circle)*, brain-stem gliomas *(diamond)*, and miscellaneous tumors *(star)*.

Table I. Characteristics of patients treated with salvage MOPP regimen

Tumor type	No.	Mean age at diagnosis (range, yr)	Gender	
			M	F
Medulloblastoma	19	7 (11/12-12)	16	3
Brain-stem glioma	16	7 (2½-3½)	6	10
Astrocytoma	13	11 (7-15)	7	6
Glioblastoma multiforme	4	11 (7-13½)	3	1
Mixed glioma, anaplastic	4	10 (7-12)	1	3
Pilocytic/ganglioglioma/unknown	5	13 (12-15)	3	2
Miscellaneous	12	5 (9/12-15)	4	8
Ependymoma	4	8 (3-15)	1	3
Primitive neuroectodermal	4	4 (8/12-12)	3	1
One case each of meningeal sarcoma, malignant meningioma, embryonal carcinoma, choroid plexus carcinoma	4	6 (9/12-13)	0	4

with astrocytomas, five patients had glioblastoma multiforme (World Health Organization criteria),[7] two had anaplastic astrocytomas, two had mixed gliomas with an aggressive astrocytic component, two had pilocytic tumors, and one had a ganglioglioma. In two cases of aggressive thalamic lesions, no tissue specimens were available. The group of miscellaneous tumors included four ependymomas (one with ependymoblastoma features), four supratentorial primitive neuroectodermal tumors, two of the pineal region, one meningeal sarcoma, one malignant meningioma, one choroid plexus carcinoma, and one embryonal carcinoma. Two patients with medulloblasto-

Table II. MOPP regimen*: Twenty-eight-day cycles for 2 years

Drug	Dosage (mg/m^2)	Cycle
Nitrogen mustard	6	Days 1, 8
Vincristine	1.4	Days 1, 8
Procarbazine	100	Days 1-10
Prednisone	40	Days 1-10, then tapered

*Dose modification for hematopoietic toxicity: Leukocytes, 3000 to 4000/mm^3: 50% of procarbazine and nitrogen mustard. Platelets >100,000/mm^3 and leukocytes, 2000 to 3000/mm^3: 25% of procarbazine and nitrogen mustard. Leukocytes, 1000 to 2000/mm^3: no procarbazine or nitrogen mustard and 50% of vincristine. Platelets, 50,000 to 100,000/mm^3: 100% of vincristine and 25% of nitrogen mustard, no procarbazine. Platelets <50,000/mm^3: no therapy.

mas had extraneural metastases, and seven had malignant cells in the subarachnoid space. Leptomeningeal spread was also documented in two patients with ependymoma and in two with primitive neuroectodermal tumors.

Treatment. Before they began MOPP therapy, all patients had complete clinical evaluations that included functional status and neurologic examination. The need for steroids and the dosages given were recorded in each case. If dexamethasone (Decadron) was initially necessary, prednisone was omitted. Each patient had a computerized axial tomography scan of the brain. Cerebrospinal fluid was examined for malignant cells whenever required and permitted by neurologic status. Laboratory examinations included complete blood cell counts plus hepatic and renal function tests.

All patients were treated with the standard MOPP chemotherapy regimen every 28 days. The regimen was modified for myelosuppression (Table II). Treatment was continued for 2 years or until disease progression developed, whichever occurred first.

Patients were followed (including full neurologic examination and CT scans of the brain) at regular intervals, usually every 3 months, or whenever symptoms recurred. Blood counts were performed at weekly intervals early in the course of treatment and then twice monthly.

The Kaplan-Meier method was used to generate actuarial curves of survival from diagnosis, survival from initiation of MOPP therapy, and time to tumor progression from start of the therapy.

Response was defined according to the criteria recommended by the American Cancer Society workshop at Niagara Falls,[7] which are different from those used previously by us. Complete response is absence of tumor on CT scan and in cerebrospinal fluid studies when applicable; partial response is CT evidence of 50% tumor mass

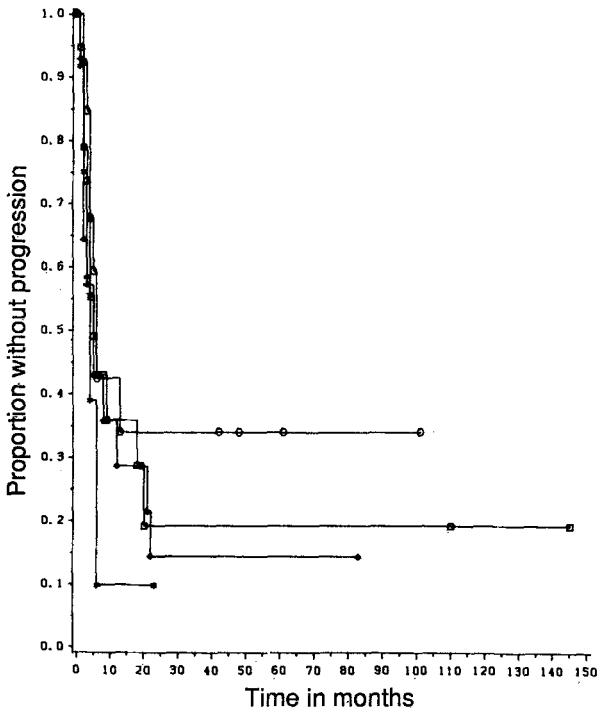

Fig. 3. Time to tumor progression on MOPP therapy for patients with medulloblastomas *(square)*, gliomas *(circle)*, brainstem gliomas *(diamond)*, and miscellaneous tumors *(star)*.

regression (measured as sum of perpendicular diameters). Stable disease or improvement is defined by tumor mass reduction of <50% as already defined. Progressive disease is an increase in tumor mass by >25%.

These radiographic criteria are not useful for evaluations of brain-stem glioma.[7] Therefore for this patient group, we used a combination of neurologic and function status, steroid dependence, and CT appearance.[7]

RESULTS

Responses of patients with various tumor types to MOPP therapy are shown in Table III. Survival from diagnosis and initiation of therapy and time to tumor progression are depicted in Figs. 1 to 5. Disease progression was halted in 14 of 19 patients with medulloblastomas. Mean time to tumor progression in 13 patients who had a relapse was 6 months (Fig. 3); yet of 12 patients followed up for more than 5 years from initiation of MOPP therapy, three have survived in complete clinical remission (12, 10, and 19 years, respectively) (Fig. 2). MOPP therapy eliminated malignant cells in only one of seven patients with medulloblastoma with leptomeningeal spread and positive cytologic findings of cerebrospinal fluid. In two patients with extraneural metastases, a femoral lesion

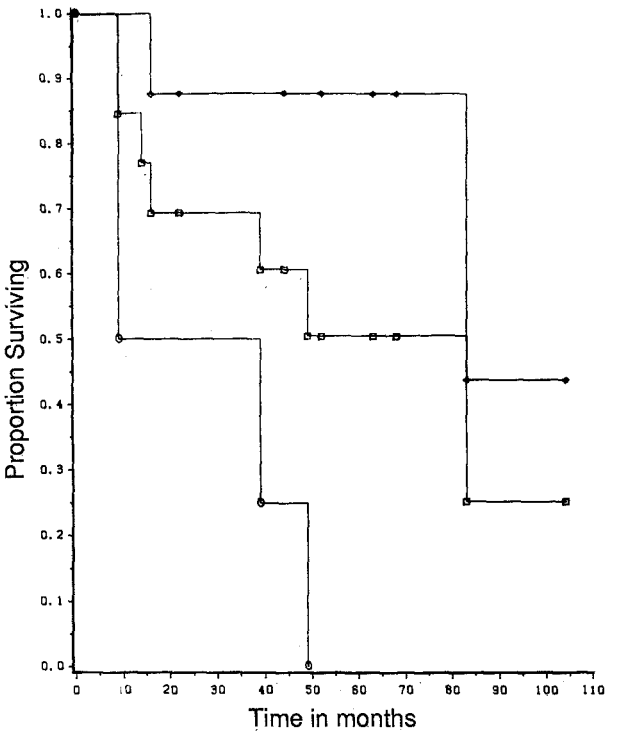

Fig. 4. Survival from the time of diagnosis of patients with glioblastomas *(circle)*, other astrocytomas *(diamond)*, and the combined group *(square)*.

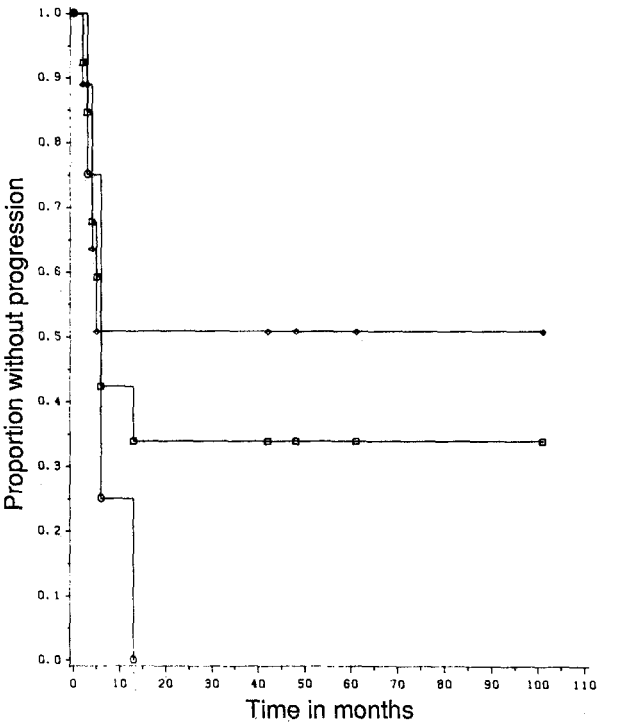

Fig. 5. Time to tumor progression of patients with glioblastomas *(circle)*, other astrocytomas *(diamond)*, and the combined group *(square)*.

Table III. Response rates of brain-tumors to salvage MOPP

Tumor type	No.	Complete remission	Partial response	Stable disease	All responses	Progressive disease
Medulloblastoma	19	1	3	10	14	5
Brain-stem glioma	16	0	3	2	5	11
Astrocytomas	13	2	2	7	11	2
Miscellaneous	12	0	2	5	7	5
Total	60	3	10	24	37	23

was markedly reduced in size by MOPP, whereas a chest mass progressed during treatment.

Mean time to tumor progression in four patients with glioblastomas was 7½ months (Fig. 5); survival from diagnosis averaged 26 months (Fig. 4). Patients with anaplastic astrocytomas or mixed gliomas with an aggressive astrocytic component fared better (Figs. 4 and 5) and two are long-term survivors (8½ and 4 years from therapy onset, respectively). One patient died 8 months after MOPP initiation, and a fourth has had a partial response and is currently receiving therapy. Among patients with lower-grade gliomas, those patients with recurrent gangliogliomas and pilocytic astrocytomas are alive 3½ and 4 years, respectively, from the beginning of therapy, but the two patients with unbiopsied thalamic lesions died 16 months after diagnosis (Figs. 4 and 5).

Response and survival of patients with brain-stem gliomas were poor. Mean time to progression was 3½ months, and only two patients survived (Figs. 1 to 3).

Of the four patients with ependymomas in the miscellaneous group, one has completed therapy and is in remission, and the others died within 6 months of MOPP initiation. For the patients with a variety of other lesions, the disease was uniformly and rapidly fatal. (Table III and Figs. 1 to 3).

The toxicity of the MOPP regimen is outlined in Table IV. Bone marrow suppression, mainly neutropenia, was common and required dose adjustment (Table II). Most

infections, such as otitis media, were mild, but two deaths occurred: one as a result of *Pneumocystic carinii* pneumonia and one as a result of a cerebral aspergilloma.

DISCUSSION

The prognosis for all patients with recurrent brain tumors remains poor. For example, in the largest reported series of 120 medulloblastomas, 82% of 35 recurrent tumors resulted in death within a year of recurrence.[8] Therefore progressively more novel and toxic therapy regimens have been advocated.[9] In general, however, results have depended more on the biologic properties of the specific tumor than on the chemotherapeutic agents.

At our institution, the MOPP regimen has been front-line therapy for recurrent brain tumors in children. The rationale is discussed extensively elsewhere.[4,5] The results confirm the marked differences in the susceptibility of various brain tumors to chemotherapy. At one end of the response spectrum are brain-stem gliomas, whose natural course has been minimally affected by chemotherapy[1,8]; our results are no exception. Similarly, the survival of our four patients with glioblastomas is no better than that reported in other series.[1,9] Among four children with anaplastic gliomas, the long-term survival of two (8 and four years) and the partial response of a third patient attest to the value of MOPP for this tumor type. Moreover, in more than 70% of patients with other aggressive recurrent tumors such as medulloblastoma, MOPP arrested disease progression. According to new stringent radiologic criteria,[7] most patients in our series fall into the stable disease category, and yet a residual tumor mass shown on a CT scan with <50% reduction in size may indicate an inactive tumor and is compatible with long-term survival. Thus three of six patients with medulloblastomas followed up for more than 10 years are in complete clinical remission with unchanged residual lesions on CT scan. Many patients in this series were enrolled before the routine use of magnetic resonance imaging. This diagnostic method may help resolve the dilemma of response definition.

Our results compare favorably with those of other large series. Crafts et al.[10] used procarbazine, lomustine, and vincristine in 17 children with recurrent medulloblastomas. Using less stringent response criteria, they reported a 62% response rate and a 31% stable disease rate. Mean time to tumor progression was 45 weeks, and there were no long-term survivors.[10] Of eight patients[11] who received vincristine, carmustine, dexamethasone, and intrathecal as well as intravenous methotrexate, one has survived for 5 years and two others were in remission at 9 and 17 months, respectively, from the time that therapy was initiated. The only other study that used the American Cancer Society response criteria[12] evaluated vincristine and cyclophosphamide for the treatment of recurrent medulloblastomas.

Table IV. Toxic reactions to MOPP regimen during 307 fully evaluable courses (71% of 398 courses administered)

Condition	No. of courses in which condition was present	% of fully evaluable courses
Total leukocytes <3000/mm³	175	57
Platelets <100,000/mm³	35	11.4
Infections	33	10.7
Procarbazine rash	2	0.6
Courses of reduced dosages	145	47

Fourteen of 16 patients manifested some response (complete, partial, or stable disease), and yet there were no long-term survivors.[12]

Preliminary results of the so-called eight-in-one regimen for recurrent brain tumors (including medulloblastoma) were recently published.[13] A 70% response rate has been claimed, and yet patient number, response criteria, survival, time to progression, or toxicity were not discussed.[13]

Toxicity of the MOPP regimen, which consisted mainly of neutropenia, resulted in dose reduction in 47% of evaluable courses, but the reductions allowed uninterrupted therapy. This compares favorably with the reported severe bone marrow toxicity,[10] which required significant dosage reductions for 15 of 16 patients.

Thus MOPP emerges as a fairly tolerable multiagent regimen for recurrent brain tumors with significant salvage potential. This chemotherapy for recurrent medulloblastomas and astrocytomas (anaplastic and low-grade) resulted in a significant number of long-term survivors. These results and the established efficacy of MOPP chemotherapy, combined with surgery, as primary treatment for brain tumors in infants,[4] especially those with medulloblastomas,[5] and the recent promising results with MOPP for adjuvant therapy for the same tumor, call for further study of MOPP in the treatment of brain tumors in children.

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