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# *Survival and Neurologic Outcome of Infants With Medulloblastoma Treated With Surgery and MOPP Chemotherapy*

## *A Preliminary Report*

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The results of treatment of infants with medulloblastoma using surgery and chemotherapy, without the use of radiation therapy, are reported. Both survival and outcome, in terms of growth, neurologic deficit, and intelligence are compared with the same parameters in children treated conventionally. Although preliminary, our results suggest that chemotherapy combined with surgery is a valid option for the treatment of infants with this type of neoplasm.

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**P** RIMITIVE NEUROECTODERMAL TUMORS of the posterior fossa, or medulloblastomas, are common and constitute between 20% and 23% of all brain tumors in the pediatric age group.<sup>1-3</sup> The incidence in infants aged less than 3 years is similar.<sup>3,4</sup> The outcome of medulloblastoma of childhood has been progressively improving during the past two decades. Initially, in Cushing's day, a 5 year survival was practically unknown. The introduction of improved surgical techniques and radiation therapy has steadily improved outcome. Currently, large centers are reporting a 50% to 75% 5 year survival in children with medulloblastoma, while the epidemiologic studies documented by the Surveillance, Epidemiology, and End Results (SEER) group suggest a 5 year survival of 39%;<sup>4</sup> the outcome is far less optimistic in the case of infants,<sup>3</sup> with 27% 1 year survival and less than 20% 5 year survival being commonly cited in the literature.<sup>3,4</sup> Moreover, there have not been any major advances in improving the outcome of this high risk group. Surgery alone, without radiation and/or chemotherapy, is associated with 100% mortality. Radiation therapy has changed this poor picture, but at the price of significant morbidity and late sequelae.<sup>3,5,6</sup> Craniospinal irradiation is associated with disruption of growth, re-

lated both to arrest of skeletal development and endocrinologic dysfunction, such as, deficiency of growth hormone.<sup>7,8</sup> Low intelligence, as measured by both performance and verbal intelligence quotients (IQ), numerous learning disabilities, and attention deficit disorders are well documented in this population.<sup>5,9</sup> Moreover, the morbidity seems to be inversely related to age, with youngsters aged less than 4 years being the most adversely affected.<sup>5,9,10</sup>

Chemotherapy has been attempted in several group studies<sup>11-13</sup> and has been shown to be of benefit in infants with medulloblastoma.

This report describes the results in nine consecutive infants with medulloblastoma, treated at the University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute.

### **Patients and Methods**

Study population consisted of nine consecutive infants, aged less than 36 months, seen and treated since August 1979. All patients had pathologically proven medulloblastoma, reviewed by the neuropathologist at our institute, and had total or subtotal resection before therapy. The patient's age at diagnosis, sex, extent of disease, and time of follow-up are documented in Table 1. Chemotherapy consisted of the methylchloroethamine, vincristine, procarbazine, and prednisone (MOPP) regimen as detailed in Table 2. Drug doses have been modified as displayed in that table. Examination of patients on presentation consisted of computed tomography

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TABLE 1. Characteristics of Infants Treated With MOPP Chemotherapy

| No./sex | Age at dx (mo) | Residual local disease on CT | CSF cytology at dx | Tumor histology |                 | Outcome | Follow-up time from dx |
|---------|----------------|------------------------------|--------------------|-----------------|-----------------|---------|------------------------|
|         |                |                              |                    | Desmoplasia     | Differentiation |         |                        |
| 1 M     | 18             | None                         | +                  | —               | None*           | Alive†  | 7 yr                   |
| 2 M     | 10             | Massive residual tumor       | N/A                | +               | None*           | Alive   | 5 yr                   |
| 3 M     | 33             | None                         | +‡                 | +               | None            | Dead§   | 19 mo                  |
| 4 F     | 12             | None                         | —                  | —               | None*           | Alive   | 3½ yr                  |
| 5 M     | 22             | None                         | —                  | +               | None            | Alive   | 3 yr                   |
| 6 M     | 16             | None                         | —                  | +               | None            | Alive   | 2 yr                   |
| 7 M     | 33             | None                         | —                  | +               | Astrocytic      | Alive   | 1 yr                   |
| 8 F     | 18             | Minimal CT enhancement       | —                  | —               | None*           | Alive   | 7 mo                   |
| 9 M     | 7              | None                         | —                  | —               | Astrocytic      | Dead    | 5 mo                   |

MOPP: methylchloroethamine, vincristine, procarbazine, and prednisone; dx: diagnosis; CT: computed tomography; CSF: cerebrospinal fluid; NA: not applicable; XRT: radiation therapy; IV: intravenous; ALL: acute lymphoblastic leukemia.

\* Immunohistochemistry not done.

† Cauda equina recurrence, received craniospinal XRT.

‡ Cleared on MOPP.

§ Recurred locally and developed ALL; died despite therapy.

|| Relapsed locally, salvaged with cisplatin.

¶ Never responded to therapy: MOPP, cisplatin, IV procarbazine, or to XRT.

(CT) of the brain, with and without contrast, supplemented more recently by magnetic resonance imaging. Patients 6 and 7 had radiographic examination of the spinal canal. Cerebrospinal fluid was tested for malignant cells, protein, glucose, microbiologic stains and, more recently, for polyamines. Disease dissemination was evaluated using bone survey and bone marrow studies.

Multiple sections of tumor from each patient were examined by light microscopy. Immunohistochemical staining of formalin-fixed, paraffin-embedded tissue was performed according to standard methods in four patients with appropriate positive and negative controls.

TABLE 2. MOPP Regimen

| Administration regimen                       |                                                               |
|----------------------------------------------|---------------------------------------------------------------|
| 28 d cycles, given for 2 yr                  |                                                               |
| Nitrogen mustard                             | 6.0 mg/M <sup>2</sup> d 1, 8                                  |
| Vincristine                                  | 1.4 mg/M <sup>2</sup> d 1, 8                                  |
| Procarbazine                                 | 100 mg/M <sup>2</sup> d 1–10                                  |
| Prednisone                                   | 40.0 mg/M <sup>2</sup> d 1–10 then tapered                    |
| Dose modification for hematopoietic toxicity |                                                               |
| WBC 3000–4000/μl                             | 50% of procarbazine and nitrogen mustard                      |
| Platelets >100,000/μl                        |                                                               |
| WBC 2000–3000/μl                             | 25% of procarbazine and nitrogen mustard                      |
| WBC 1000–2000/μl                             | No procarbazine or nitrogen mustard; 50% of vincristine       |
| Platelets 50,000–100,000/μl                  | Vincristine 100% and 25% of nitrogen mustard; no procarbazine |
| Platelets <50,000/μl                         | No therapy                                                    |

WBC: leukocyte count.

Polyclonal antibodies to glial fibrillary acidic protein (GFAP) and monoclonal antibodies to neurofilament protein 200 kd (NF) were used in all four, and antibodies to vimentin, S-100 protein, or neuron-specific enolase were sometimes applied. Differentiation was defined as reactivity of cytoplasm and/or processes of neoplastic cells with antiGFAP or antiNF. Neurologic examinations were conducted at our institute on presentation and on follow-up visits.

Developmental assessments were completed on all surviving patients followed by us (five) using a modified version of the Denver Developmental Screening Test. Additional testing of adaptive behavior, using the Vineland Adaptive Behavior Scales (two), and of cognitive abilities, using the McCarthy Scales of Children's Abilities (one), were completed on two infants. A comprehensive assessment using the Vineland and Wechsler Intelligence Scales for Children-Revised was obtained for Patient 1 who had also received craniospinal irradiation.

## Results

The survival of infants with medulloblastoma, treated with surgery and MOPP chemotherapy is displayed in Figure 1. This survival curve depicts a 1 year survival of 88% and a projected 5 year survival of 77%. Currently, seven of nine infants are alive, four of whom are more than 3 years from diagnosis, *i.e.*, more than 1 year after termination of therapy, and are in complete and sustained remission. One of the survivors had had a relapse and was given craniospinal irradiation (CSI) at the age of 37 months. This patient, because of his CSI, was excluded from investigations of neurologic outcome,

growth, and neuropsychologic evaluation. A second patient, surviving for more than 4 years from time of diagnosis, had relapsed 3 months after diagnosis and was salvaged using cisplatin. She is included in the neurologic and growth evaluation. The two deaths occurred less than 6 months and 20 months, respectively, after diagnosis. The first, an infant aged 7 months at time of diagnosis, had relentless progressive disease, unresponsive to two surgical procedures, cranial irradiation, and various chemotherapy regimens, including MOPP, carboplatin, and continuous-infusion intravenous procarbazine. The second infant, while on his MOPP regimen, developed local disease recurrence as well as acute lymphocytic leukemia and died.

Tumor desmoplasia and differentiation are shown in Table 1. No tumor showed evidence of ependymal, oligodendroglial, or neuronal differentiation with routine light microscopy or special immunohistochemical stains. Astrocytic differentiation in the two cases indicated was focal, but definite, involving moderate numbers of neoplastic cells.

Table 3 shows the neuropsychologic and neurologic status and growth parameters of the surviving infants. Of six evaluable survivors, five display cerebellar findings related to the original disease. Motor function as measured by tone, strength, and tendon reflexes is intact in four of six survivors, one is abnormal, and one has not been followed at our institution. Neuropsychologic assessment of the six survivors not given craniospinal irradiation reveals average range performance on the majority of developmental and adaptive behavior measures. On the Denver Developmental Screening Test, four of five patients tested have developmental quotients greater than 90%; the other is mildly retarded. Vineland Adaptive Behavior Composite scores for the two children who had received comprehensive assessments are 113 and 88 (this patient has motor incoordination with motor domains scaled score = 77, and general cognitive abilities = 115). In contrast, Patient 1 who had received craniospinal irradiation exhibits global impairments (Wechsler verbal IQ = 60, and performance IQ = 87) that were not apparent during early development. Findings also indicate significant deficits on the Vineland domains of communication (score = 52), daily living skills (score = 37), and socialization (score = 69). Growth of four of six surviving infants is within normal range, being more than 20th percentile for height and weight.

### Discussion

Medulloblastomas account for approximately 20% of all brain tumors in infants and children. This malignant posterior fossa tumor, uniformly fatal in the past, now carries a 50% survival in academic centers.<sup>1-4</sup> More re-

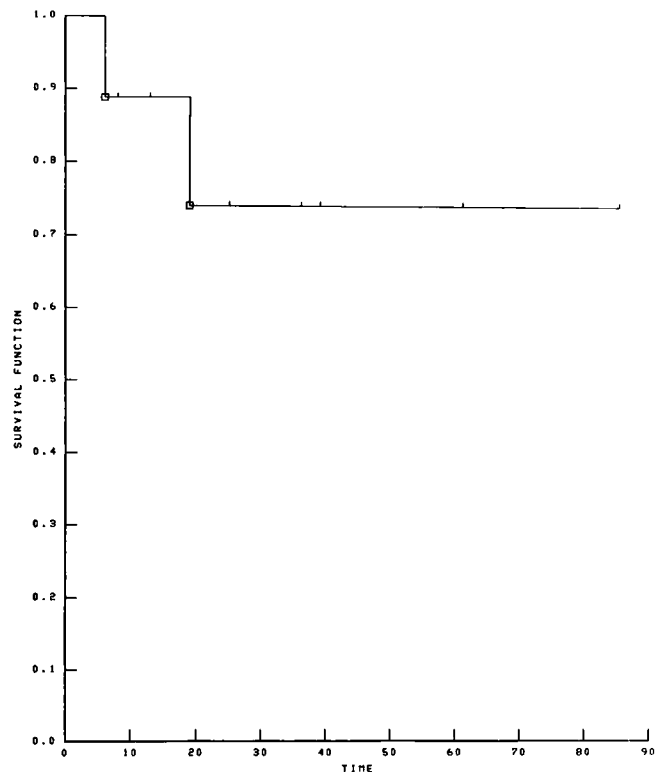


FIG. 1. Survival curve for nine infants with medulloblastoma (Kaplan-Meier method). Censored = alive (seven); uncensored = dead (two); squares indicate time of death; short vertical lines indicate length of follow-up.

cently, high risk groups with much lower survival rates have been identified,<sup>3,4</sup> one major group being infants. Thus, an age at onset of less than 3 years is associated with a 1 year survival rate of 27% and a projected 5 year survival rate of less than 18%.<sup>4</sup> The cause for the decreased survival in infants with medulloblastoma is not clear. A popular hypothesis, assuming the onset of all medulloblastomas *in utero*, suggests that medulloblastomas in infants are more aggressive as manifested by their earlier appearance and diagnosis. A second possibility relates to the less aggressive therapy received by

TABLE 3. Growth and Neurologic Outcome of Survivors of Medulloblastoma Treated With Resection and MOPP (no. = 6)\*

|                          | Normal | Abnormal | Unknown† |
|--------------------------|--------|----------|----------|
| Neuropsychologic exam†   | 4/6    | 1/6      | 1/6      |
| Neurologic exam          |        |          |          |
| Motor                    | 4/6    | 1/6      | 1/6      |
| Cerebellar               | 1/6    | 3/6      | 2/6      |
| Height > 20th percentile | 4/6    | 1/6      | 1/6      |
| Weight > 20th percentile | 4/6    | 1/6      | 1/6      |

\* Seventh survivor received craniospinal irradiation.

† Followed elsewhere, not seen for >1 yr, or not recorded.

‡ See text for detailed testing parameters.

infants, poor tolerance to chemotherapy, and/or doses of radiation smaller than conventionally employed.

Furthermore, the morbidity in infant survivors with medulloblastoma is very significant. Numerous investigators including Li *et al.*,<sup>14</sup> Raimondi and Tomita,<sup>5</sup> and Spunberg *et al.*<sup>15</sup> have documented the poor functional outcome of survivors. Mainly affected are intelligence, as measured by developmental quotient, performance and verbal IQ, growth, and general adjustment in school and in society. Thus, of six infants with medulloblastoma in Raimondi and Tomita's study, only two are more than 10th percentile in height, only two are in regular school, and three have major neurologic problems such as hemiplegia and blindness. This is unfavorably compared with youngsters with posterior fossa tumors not necessitating radiation such as cerebellar astrocytomas (all in regular school, all with normal height, 75% with normal neurologic examination).

Chemotherapy, in conjunction with radiation therapy, has been shown to be effective in selected high risk groups of youngsters with medulloblastoma, specifically those with younger age at onset. Both the Children's Cancer Study Group (CCSG) study,<sup>11</sup> as well as the summary of the International Society of Pediatric Oncology (SIOP) group<sup>12</sup> suggest an increased survival rate of infants treated with chemotherapy compared with those given radiation therapy alone following surgery. Moreover, recent unpublished data from the Pediatric Oncology Group (POG) studies comparing the using of MOPP chemotherapy as an adjuvant in children with medulloblastoma with conventional therapy (surgery followed by radiation) alone suggest a better outcome for youngsters receiving chemotherapy.<sup>13</sup>

In this study we elected to use the MOPP regimen. The rationale for using this drug combination is as follows:

Each of the major components of this regimen, *i.e.*, nitrogen mustard,<sup>16</sup> vincristine,<sup>17,18</sup> and procarbazine<sup>19</sup> has been shown independently to be effective against brain neoplasms. The toxicity spectrum and range of this particular combination have been well documented throughout its extensive use for youngsters with Hodgkin's disease.<sup>20</sup> Moreover, in a Phase II study in infants with brain tumors, MOPP was well tolerated.<sup>21</sup> The toxicity is mainly hematologic and may necessitate reduction of the dose. We have had no major bleeding episodes or deaths related to this regimen in our group, and most infants tolerated it well. Infections constituted the major adverse sequel of this drug regimen.

Despite the fact that the main aim of the current study was to eliminate the morbidity associated with radiation therapy and not necessarily decrease mortality, the survival data of the nine infants reported are encouraging.

The reasons underlying the improved survival of the nine infants are not immediately clear. Histology, dissemination of disease preoperatively and postoperatively, as well as treatment and statistical chance, may all be contributing factors.

A diverse spectrum of histologic subtypes of medulloblastoma was included in this group of neoplasms; several were desmoplastic variants. However, this type has been claimed to portend either a better<sup>22</sup> or a worse<sup>23</sup> prognosis. The presence of cell differentiation and its relation to prognosis is also under close scrutiny. Two recent studies have claimed either an improved<sup>24</sup> or a decreased<sup>25</sup> recurrence-free survival period with evidence of cell differentiation in medulloblastoma. Our results do not clearly correlate with either view. Thus, no histopathologic features can adequately account for the apparently favorable behavior of this group of patients.

As depicted in Table 2, two thirds of the surviving infants with medulloblastoma, who have not undergone radiation therapy, have growth rates which are within the normal range and no major neurologic deficits. The only neurologic deficit, manifested by cerebellar dysfunction, may well be related to the nature and location of the primary tumor. Virtually no deficit attributable to the therapy has been evident.

Neuropsychologic assessment results indicate few, if any, deficits in high order cognitive functions among children treated with MOPP chemotherapy alone. Language skills, which are the best predictors of cognitive development among infants, were found to be within the average to superior range for the two children who received comprehensive assessments. The deficits observed on measures of motor skills and coordination probably correlate with the original disease and the findings on the neurologic examination. In contrast, the patient who received craniospinal irradiation manifested global impairments.

Thus, it appears that surgical intervention, followed by the MOPP regimen of chemotherapy, without institution of craniospinal irradiation, may be a reasonable and satisfactory option in the treatment of infants with medulloblastoma.

#### REFERENCES

1. Chutorian AM, Ganti SR. Diagnosis of intracranial tumors in infants and children. In: Chang LCH, Housepinn EM, eds. Tumors of the Central Nervous System. New York: Masson Publishing USA, 1981; 83-106.
2. Walker RW, Allen JC. Pediatric Brain Tumors. *Pediatr Ann* 1983; 12:5:383-394.
3. Cohen ME, Duffner PK. Brain Tumors in Children: Principles of Diagnosis and Treatment. New York: Raven Press, 1984.
4. Duffner PK, Cohen ME, Myers MH, Heise HW. Survival of children with brain tumors: SEER Program 1973-1980. *Neurology* 1986; 36:597-601.
5. Raimondi AG, Tomita T. The disadvantages of prophylactic

whole CNS postoperative radiation therapy for medulloblastoma. In: Paoletti P, Walker MD, Butler G, Kuerick R, eds. *Multidisciplinary Aspects of Brain Tumors*. New York: Elsevier North-Holland, 1979; 209-218.

6. Poplack DG, Brouwers P. Adverse sequelae of central nervous system therapy. *Clinics in Oncology* 1985; 4:2:263-284.

7. Shalet SM, Beardwell CG et al. Growth hormone deficiency in children with brain tumors. *Cancer* 1976; 37:1146-1149.

8. Shalet SM, Beardwell CG. Endocrine consequences of treatment of malignant disease in childhood: A review. *J R Soc Med* 1979; 73:34-45.

9. Silverman CL, Thomas PRM, Palkes H, Kovnar E, Talenk B, Bedwinck JM. Late psychological and intellectual effects on patients and their families following definitive radiotherapy for childhood medulloblastoma (Abstr). *Proc Am Soc Clin Oncol* 1982; 1:49.

10. Mulhern RK, Kun LE. Neuropsychologic function in children with brain tumors: III. Interval changes in the 6 months following treatment. *Med Pediatr Oncol* 1985; 13:318-324.

11. Cohen ME, Duffner PK. *Brain Tumors in Children: Principles of Diagnosis and Treatment*. New York: Raven Press, 1984.

12. Bloom HJG. Intracranial tumors: Response and resistance to therapeutic endeavors. *Int J Radiat Oncol Biol Phys* 1982; 8:1083-1113.

13. Pediatric Oncology Group 7909. Preliminary analysis. St. Louis: Proceedings Pediatric Oncology Meeting, 1986.

14. Li FP, Winston KR, Gimbere K. Follow-up of children with brain tumors. *Cancer* 1984; 54:135-138.

15. Spunberg JG, Chong CH, Goldman M, Auricchio E, Bell JG. Quality of long-term survival of following irradiation for intracranial tumors in children under the age of two. *Int J Radiat Oncol Biol Phys* 1981; 7:727-736.

16. Cangir A, Ragab AH, Steuber P, Land VJ, Berry DH, Krischer JP. Combination chemotherapy with vincristine, procarbazine, and prednisone with or without nitrogen mustard in children with recurrent brain tumors. *Med Pediatr Oncol* 1984; 12:1-3.

17. Lassman LP, Pearce GW, Gary G. Sensitivity of intracranial gliomas to vincristine sulfate. *Cancer* 1968; 1:296-297.

18. Liss L. The use of tissue cultures in the study of brain tumors. In: Bingham WG Jr, ed. *Recent Advances in Brain Tumor Research: Progress in Experimental Tumor Research*, 17. Basel: S. Karger, 1972; 93.

19. Crafts DC, Levin VA, Edwards MS, Fischer TL, Wilson CB. Chemotherapy of recurrent medulloblastoma with combined procarbazine, CCNU, and vincristine. *J Neurosurg* 1978; 49:589-592.

20. Young RC, Devita VT, Johnson RE. Hodgkin's disease in childhood. *Blood* 1973; 42:163-179.

21. van Eys J, Cangir A, Coody D, Smith B. MOPP regimen as primary chemotherapy for brain tumors in infants. *J Neuro-oncol* 1985; 3:237-243.

22. Chatty EM, Earle KM. Medulloblastoma: A report of 201 cases with emphasis on the relationship of histologic variants to survival. *Cancer* 1971; 28:977-983.

23. Park TS, Hoffman HJ, Hendrick EB et al. Medulloblastoma: Clinical presentation and management: Experience at the Hospital for Sick Children, Toronto, 1950-1980. *J Neurosurg* 1983; 58:543-552.

24. Caputy AJ, McCullough DC, Manz HJ et al. A review of the factors influencing the prognosis of medulloblastoma. *J Neurosurg* 1987; 66:80-87.

25. Packer RJ, Sutton LN, Rorke LB et al. Prognostic importance of cellular differentiation in medulloblastoma of childhood. *J Neurosurg* 1984; 61:296-301.