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Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy

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It has previously been reported in a single-institution trial that progression-free survival of children with medulloblastoma treated with radiotherapy and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), cisplatin, and vincristine chemotherapy during and after radiotherapy was better than the outcome in children treated with radiotherapy alone. To better characterize long-term outcome and duration of disease control, this treatment approach was used for 10 years and expanded to three institutions. Sixty-three children with posterior fossa medulloblastomas were treated with craniospinal local-boost radiotherapy and adjuvant chemotherapy with vincristine weekly during radiotherapy followed by eight 6-week cycles of cisplatin, CCNU, and vincristine. To be eligible for study entry, patients had to be older than 18 months of age at diagnosis and have a subtotal resection, evidence of metastatic disease, and/or brainstem involvement. Patients younger than 5 years of age and without these poor risk factors who received reduced-dose craniospinal radiotherapy (2400 cGy) were also eligible for entry into the study. Sixty-three of 66 eligible patients (95%) were entered and placed on this treatment regimen. Forty-two patients had brainstem involvement, 15 had metastatic disease at the time of diagnosis, and 19 had received a subtotal resection. Progression-free survival for the entire group at 5 years is 85% ± 6%. Three children have succumbed to a second malignancy, and overall 5-year event-free survival is 83% ± 6%. Progression-free survival was not adversely affected by younger age at diagnosis, brainstem involvement, or subtotal resection. Five-year actuarial progression-free survival for patients who received reduced-dose radiotherapy was similar to that for patients receiving conventional-dose radiotherapy. Patients with metastatic disease at the time of diagnosis had a 5-year progression-free survival rate of 67% ± 15%, as compared to 90% ± 6% for those patients with localized disease at the time of diagnosis ($p = 0.037$). The authors conclude that overall progression-free survival remains excellent for children with posterior fossa medulloblastomas treated with this drug regimen. Chemotherapy has a definite role in the management of children with medulloblastoma. Further studies are indicated to define which subpopulations of children with medulloblastoma benefit from chemotherapy and what regimens are optimum in increasing disease control and, possibly, in reducing the amount of radiotherapy required.

KEY WORDS • brain neoplasm • medulloblastoma • primitive neuroectodermal tumor • chemotherapy • radiotherapy • children

MANAGEMENT of medulloblastoma/primitive neuroectodermal tumor (MB/PNET), the most common primary central nervous system (CNS) tumor of childhood, has slowly evolved over the past four decades.[4,7,8,16,18,20,21] The biology of MB/PNET remains poorly understood and controversy still exists concerning the best way to classify all small, round cell tumors of the CNS including those of the posterior fossa, classically termed medulloblastoma.[25,26] Nonetheless, there has been an apparent overall increase in the disease-free survival rate for children with this tumor.[7,18,24] With currently available means of surgical removal, postoperative care, and after treatment with craniospinal and local-boost

radiotherapy, between 50% and 60% of children with MB/PNET of the posterior fossa are expected to be alive and free of progressive disease 5 years following diagnosis.[4,7,8,24] Two prospective randomized trials have suggested that the addition of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and vincristine chemotherapy during and after radiation therapy increases progression-free survival for subsets of children with MB/PNET, as compared to treatment with craniospinal irradiation alone.[4,18,28] In these studies, patients who benefited from the addition of chemotherapy included those with larger primary tumors and disseminated disease at the time of diagnosis.[4,28] At the same time, adjuvant chemotherapy has not been shown to improve the frequency or duration of progression-free survival for those patients with localized, gross totally resected MB/PNET.

In 1983, a study was begun adding cisplatin to the CCNU and vincristine chemotherapy regimen found to be of benefit in prospective randomized adjuvant chemotherapy trials.[21] This treatment approach was limited to children who were at highest risk for disease relapse after treatment with radiation therapy alone, including those patients with subtotally resected tumors, infiltration of the brain stem at the time of diagnosis, and/or neuroradiographic or cerebrospinal fluid (CSF) cytological evidence of disseminated disease. The results reported with this three-drug regimen were encouraging, and in 42 patients treated between 1983 and 1989, actuarial 5-year disease-free survival rates were greater than 85%. In comparison with a historical control group treated at the same institution between 1975 and 1983, disease control was better in children who received the three-drug adjuvant regimen than for those children treated with radiotherapy alone or radiotherapy plus a two-drug regimen of CCNU and vincristine. Despite the reported outcome, results were viewed somewhat skeptically because patients had been treated at only one institution and the median follow-up period was 40 months, with only 12 patients being followed for more than 5 years. To better characterize outcome, duration of disease control, and toxicity of treatment for children with MB/PNET treated with craniospinal irradiation and the three-drug regimen, the treatment trial was expanded to three institutions and their affiliates. This paper describes outcomes in 63 consecutive children with MB/PNET treated over the past 10 years.

TABLE 1

*Chang staging system for posterior fossa medulloblastoma**

Stage	Definition
tumor	tumor < 3 cm in diameter & limited to the midline
T_1	position in the vermis, roof of the fourth ventricle, and (less frequently) to the cerebellar hemispheres
T_2	tumor ≥ 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T_3:	tumor invading two adjacent structures or completely
T_{3a}	filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus
T_{3b}	tumor arising from the floor of the fourth ventricle of brain stem and filling the fourth ventricle
T_4	tumor further spreading through the aqueduct of Sylvius to involve the third ventricle of midbrain, or tumor extending to the upper cervical cord
metastasis	
M_0	no evidence of gross subarachnoid or hematogeneous metastasis
M_1	microscopic tumor cells found in cerebrospinal fluid
M_2	gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M_3	gross nodular seedings in the spinal subarachnoid space
M_4	extraneural metastasis

* Derived from classification system of Chang, *et al.*[2]

Clinical Material and Methods

Children between the ages of 2 and 21 years who presented to the Children's Hospital of Philadelphia, Children's National Medical Center in Washington, DC, or Children's Medical Center, Dallas, with newly diagnosed posterior fossa MB/PNET were eligible for treatment. The study opened in Philadelphia in 1983, and in Washington and Dallas in 1988. It closed for entry at Children's Hospital of Philadelphia in January of 1991 when a new study was begun using similar chemotherapy, but changing the radiotherapy to a hyperfractionated sequence. The study remained open in Washington and Dallas and was scheduled to close in late 1993.

Patients enrolled in the study at these three institutions were managed in a uniform fashion. All patients underwent posterior fossa decompression and exploration with the goal of total surgical resection. At the time of surgery, the size of the tumor was graded by the surgeon on a scale of 1 to 4 according to the classification of Chang and associates[2] (Table 1). Within 72 hours of surgery, patients underwent a contrast-enhanced computerized tomography (CT) or magnetic resonance (MR) imaging study to assess the extent of residual disease. Based on the surgeon's impression at the time of surgery and the postoperative MR or CT study, tumor resections were graded as: 1) total or near total (no areas of residual lump disease or only residual tumor rim enhancement); 2) partial (residual lump disease but less than 50% of the original tumor mass); or 3) subtotal or biopsy (less than 50% tumor resection). Seven to 14 days after surgery, myelography and/or spinal MR imaging, with and without gadolinium enhancement, was performed to assess the extent of tumor dissemination. More recently, preoperative spinal MR imaging with and without gadolinium enhancement was used in some patients instead of postoperative evaluations. Radiological findings were based on interpretations done at the participating institutions; a central review of these findings was not performed. All patients also had a CSF examination with-

in 3 weeks of surgery for determination of free-floating tumor cells. If the results of myelography and/or spinal MR imaging were normal but free-floating tumor cells were found in the CSF, a repeat lumbar puncture was performed 21 days after operation and the results from this analysis were used for designation of the metastasis stage. Based on these results, a metastasis stage, according to the Chang classification[2] (Table 1), was designated for all patients.

Eligibility Criteria

Children who underwent surgery for primary posterior fossa MB/PNET at each of the institutions or their affiliates were eligible for study entry. Eligibility was determined by the treating physician at each institution. Initially, patient entry was limited to those patients with either brainstem involvement at the time of diagnosis, subtotally resected tumors (a partial resection or a biopsy), and/or disseminated disease at the time of diagnosis. Beginning in 1987, children less than 5 years of age who were treated with reduced-dose craniospinal radiotherapy (2340 cGy) were also eligible for study. One institution (Dallas) also entered patients in the study who had large (T_4), gross totally resected, nondisseminated tumors which did not invade the brain stem. Results in these four patients were included in this analysis, although the other participating institutions did not include such patients. These four patients had Chang classified T_4 tumors with spreading outside the fourth ventricle to involve the third ventricle or upper cervical cord. It is unclear whether these tumors represented total or subtotal resections given their extensive nature, but the individuals harboring these tumors were considered nondisseminated (M_0), totally resected, T_4-stage patients for purposes of analysis. The study was approved by the Institutional Review Boards of all participating institutions. All eligible patients or their guardians had to sign informed consent prior to entry in the study.

Treatment Protocol

Radiation therapy was begun within 28 days of surgery. The radiation dose utilized for patients receiving full-dose craniospinal radiation therapy was 3600 cGy to the craniospinal axis; this was followed by an 1800- to 1980-cGy boost of radiation to the local tumor site (up to a total dose of 5400 to 5580 cGy). Patients treated with reduced-dose radiotherapy received 2340 cGy to the craniospinal axis followed by a local tumor site boost of 2700 to 3240 cGy (local tumor site dose 5040 to 5580 cGy). Daily fractions of 180 cGy were used. In the posterior fossa boost field, the treatment field included the entire tentorium with the anterior aspect of the field extending to the posterior clinoid process. The area of spinal or cranial metastatic lump disease received a local boost up to a total dose of 4500 cGy.

The chemotherapy consisted of three agents, vincristine, CCNU, and cisplatin (Fig. 1). During radiotherapy, weekly vincristine was given at a dose of 1.5 mg/sq m (up to maximum dose of 2 mg). Six weeks following completion of radiation therapy, patients were started on a regimen of CCNU at 75 mg/sq m, cisplatin at 68 mg/sq m every 6 weeks, and vincristine at 1.5 mg/sq m (up to a maximum dose of 2 mg) weekly for 3 consecutive weeks. Eight 6-week cycles of chemotherapy were planned.

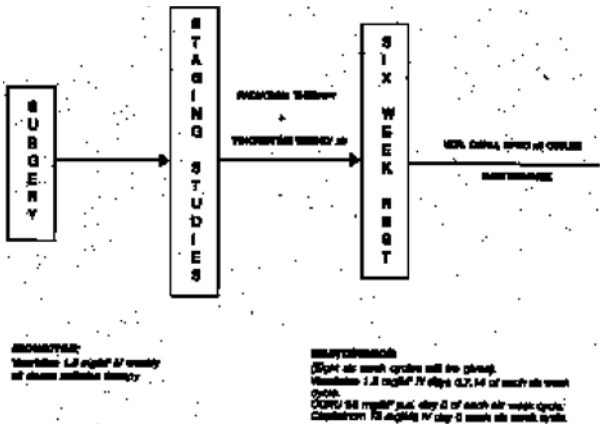

FIG. 1. Diagram illustrating the treatment protocol utilized in this study. VCR = vincristine; CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CPDD = cisplatin.

All patients underwent a formal audiological examination and renal monitoring (glomerular filtration rate or creatinine clearance) before each cycle of chemotherapy. A contrast-enhanced CT or MR study was performed every 3 months (after every two cycles of therapy) while the patient was receiving treatment and at 6-month intervals thereafter for the first 3 years after treatment. Myelography, CSF, and enhanced MR imaging of the spine in patients without metastatic disease at diagnosis were only performed if there was clinical suspicion of leptomeningeal tumor recurrence. In those patients with metastatic disease at diagnosis, CSF cytology and spinal neuroimaging were performed 6 weeks following radiotherapy and at 3-month intervals thereafter until there was complete disappearance of disseminated disease. Studies were also repeated at the completion of chemotherapy.

Toxicity-Related Dose Adjustments

The chemotherapy dosage was modified if there was any evidence of significant audiological, renal, hematological, or neural toxicity. The cisplatin dosage was reduced by 50% if there was a 20-dB hearing loss in the 50- to 3000-Hz range, if there was a 40 dB or greater loss in the 4000- to 8000-Hz hearing range, or if a 25% to 49% reduction in renal function occurred (Grade 3 toxicity). If hearing loss was greater than 20 dB in the 50- to 3000-Hz range or if loss of renal function was greater than 50%, the cisplatin was omitted for that cycle and only given thereafter if renal or hearing function improved (Grade 4 toxicity). The CCNU dosage was reduced by 50% if there was marked thrombocytopenia (platelet count $<$ 50,000/cu mm) or symptomatic neutropenia (absolute

TABLE 2
Clinical Characteristics in 63 patients

Characteristic	No. of Cases/Factors
age, mean (median) yrs	9.0 (9)
range yrs	1.5–21
sex (M/F)	41/22
T stage	
T_{3a}	15
T_{3b}	42
T_4	6
M stage	
M_0	48
M_1	4
M_{2-3}	11
resection	
total/near total	44
subtotal	19

neutrophil count < 500/cu cm with associated fevers) or evidence of infection requiring hospitalization (Grade 3–4 toxicity). The vincristine dosage was reduced by 50% if severe symptomatic paresthesias developed and was omitted for at least one dose for ileus or weakness greater than Grade 1 on a 1 to 5 grading system, and begun again when the weakness improved or the ileus resolved (Grade 3–4 toxicity).

Patient Population

As of July, 1993, 92 patients between the ages of 1.5 and 21 years with posterior fossa medulloblastoma were diagnosed during the time the study was open at the cooperating institutions (Table 2). Of these 92, 63 were treated using the study criteria outlined above. Of the remaining 29, 13 were found to have nondisseminated, totally resected disease that was confined to the posterior fossa and did not involve the brain stem; these individuals were not eligible for study and were treated with radiation therapy alone. Ten children between the ages of 1.5 years and 5 years with nondisseminated, totally resected tumors underwent a treatment protocol utilizing a further reduced dose of craniospinal irradiation (1800 cGy) and identical chemotherapy (seven of 10 patients remain alive, free of progressive disease). Due to this reduced dose of craniospinal irradiation, they were excluded from this analysis; results on these patients have been previously published. Three patients died in the immediate postoperative period. One child became dependent on a ventilator because of postoperative complications and could not be started on treatment within 28 days of surgery and, thus, is excluded from analysis. (This patient was started on treatment 42 days from diagnosis and remains alive and well, 2 years following identical radiation and chemotherapeutic treatment.) Two patients refused treatment (one remains alive, the other died). Excluding the 10 young patients treated on the reduced-dose (1800 cGy) craniospinal radiation therapy protocol and the three patients who died in the immediate postoperative period, 63 of 66 (95%) consecutively eligible patients underwent the study treatment protocol. The patient cohort was a mean of 9 years of age at the time of diagnosis and has been followed for a median of 59 months.

Statistical Considerations

Progression-free survival rate was measured from the date the patient entered the study to date of progressive disease or last contact. Patients who experienced a second malignancy were censored at the date of diagnosis of the second malignancy. Event-free survival was measured from the date of initial treatment to the date of failure, without regard to the type of failure or date of last contact. Distributions of progression-free survival and event-free survival were estimated using the technique of Kaplan and Meier[12] and comparisons were made using a Mantel-Haenszel statistic.[15] Standard errors of the Kaplan-Meier estimates were calculated with the technique proposed by Peto and coworkers.[23] Due to the small number of failures, the statistically negative findings relative to potential prognostic factors should not be interpreted as unimportant factors, but rather as an indication that this study has little power for detecting these possible correlations.

Results

There are 55 of 63 (87.3%) patients presently alive and free of progressive disease. Kaplan-Meier estimation of progression-free survival at 3 years is 90% ± 4% and at 5 years is 85% ± 6% (Fig. 2 *left*). Three children have developed and succumbed to a second malignancy. Thus, progression-free survival is better than event-free survival, which is 90% ± 4% at 3 years, 83% ± 6% at 5 years, and 72% ± 13% at 9 years (Fig. 2 *right*).

Over the study period, eight (13%) patients have developed progressive disease. The sites of failures were local in three, isolated leptomeningeal dissemination in three, and leptomeningeal and local disease in two. No child has developed extraneural disease at the time of first relapse.

Progression-free survival was not adversely affected by younger age at diagnosis, brainstem involvement, subtotal resection, or reduced-dose craniospinal irradiation. The 5-year actuarial survival rate for the small number of patients who received reduced-dose (2340 cGy) radiotherapy was 83% ± 20% as compared to 83% ± 6% for those receiving conventional (3600 cGy) radiotherapy ($p = 0.62$) (Fig. 3 *left*). Patients with metastatic disease at the time of diagnosis had a 5-year progression-free survival rate of 67% ± 15% as compared to 90% ± 6% for those patients with localized disease at diagnosis ($p = 0.037$) (Fig. 3 *right*).

Of the three patients who developed a second neoplasm, one child with a totally resected T_{3B} tumor, who was 5 years of age at the time of the first diagnosis, developed a brainstem glioma 41 months after ini-

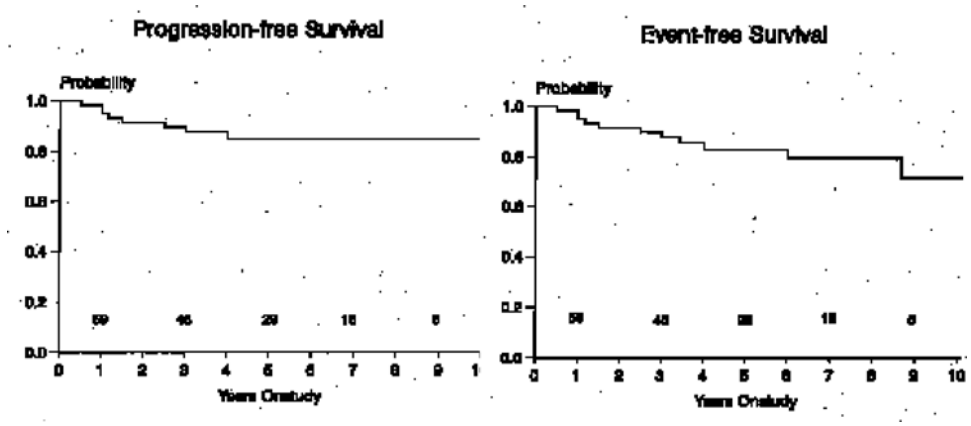

FIG. 2. Graphs depicting progression-free survival *(left)* and event-free survival *(right)* rates for all children treated.

tial treatment. Another child with a T_{3B} partially resected tumor, who was 6 years of age at the time of diagnosis, developed a glioblastoma multiforme of the posterior fossa 104 months following initial treatment. These pathologies were reviewed by the study pathologist and compared to the tissue obtained at the time of original surgery. The third child died of acute myelogenous leukemia 72 months following diagnosis.

Toxicity of the Chemotherapeutic Regimen

Occurrences of Grade 3 or 4 audiological, renal, hematological, or neural toxicity (peripheral neuropathy) are as summarized in Table 3. Thirty of 63 (47.6%) patients developed significant audiological toxicity, usually occurring after the fourth dose of cisplatin. Despite this high degree of audiological toxicity, only one child required a hearing aid at the end of treatment and another developed a progressive hearing loss 3 years following completion of treatment and now requires a hearing aid. Although Grade 3 to 4 renal toxicity was documented in 13 patients, no child has yet developed clinically significant kidney dysfunction. Grade 3 or 4 hematological toxicity was noted during 33 of the cycles of chemotherapy, which included thrombocytopenia requiring platelet transfusions in 11. However, there was no significant morbidity or mortality associated with the toxicity noted.

Severe vincristine-related peripheral neuropathy was relatively infrequent; only six patients developed either ileus or clinically significant weakness. In the two cases of ileus, there was spontaneous improvement, and vincristine could be restarted at a lower dose. Three patients had treatment-limiting vincristine-related problems. No seizures or other neurotoxicity was noted due to vincristine or any of the other drugs utilized.

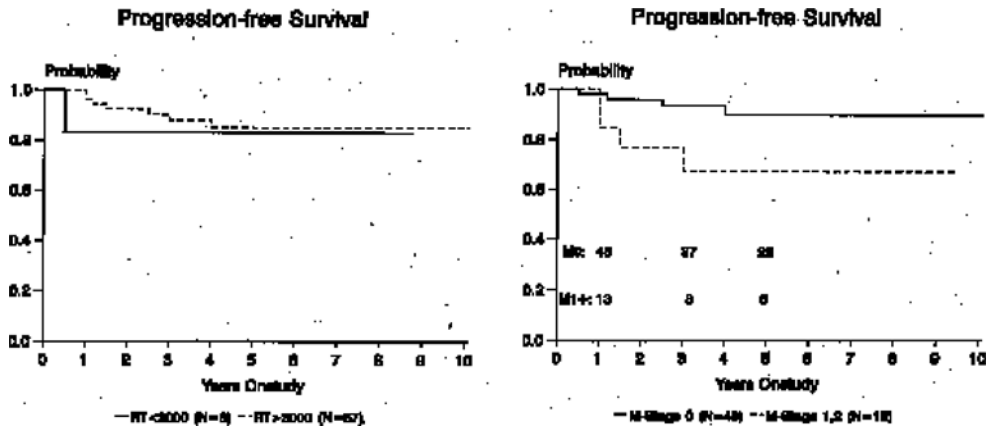

FIG. 3. Graphs showing progression-free survival rates for patients receiving reduced (2340 cGy) and conventional (3600 cGy) craniospinal radiotherapy *(left)*. *Solid line* indicates radiation treatment (RT) of less than 3000 cGy in six patients. *Broken line* indicates RT of greater than 3000 cGy in 57 patients. Graph showing progression-free survival rates for patients with and without leptomeningeal disease at diagnosis*(right)*. *Solid line* indicates M-stage 0 (48 patients), and *broken line* indicates M-stages 1 and 2 (15 patients).

TABLE 3
*Types of grade 3 to 4 toxicity**

Type of Toxicity	Chemotherapy Cycle								Total
	1	2	3	4	5	6	7	8	
hematological	5	3	3	6	5	4	5	3	33
audiological					7	14	5	3	29
renal			1		4	1	8	0†	13
neurological	3	2	1	1	3	2	2	2	16

* See text for explanation, denotes development of new toxicity or grade of toxicity.
† Not a routine test.

Thirty-five patients required some modification or omission of the cisplatin dosage during treatment. Sixty of the 63 patients received full-dose cisplatin therapy until the fifth cycle of treatment; 11 patients required a reduction in the fifth and subsequent cycles of cisplatin, 14 an initial reduction in the sixth or subsequent cycles of cisplatin, seven an initial reduction in the seventh and subsequent doses of cisplatin, and three an initial reduction in the eighth dose of cisplatin. Because of cisplatin toxicity, 15 patients were treated with less than eight cycles of cisplatin therapy. Thus, 28 of 63 (44%) could receive the full prescribed dose of cisplatin, the remainder requiring a modification of the dose or number of treatments received. The CCNU-related hematological toxicity was less predictable. Nine patients required a reduction in the dose of CCNU during one or more cycles due to toxicity. Vincristine-related peripheral neuropathy necessitated a reduction of treatment in 16 patients; however, in all but three patients vincristine could be restarted at a lower or the original dose after omitting the drug for 1 to 2 weeks.

Discussion

Natural History and Survival

The 5-year progression-free survival rate of 85% and the 5-year event-free survival rate of 83% in the 63 patients presented confirms the excellent survival rates previously reported for children treated with this radiation and chemotherapy regimen over the past 12 years and compares favorably to other reported series.[21] The reasons for the present report deal primarily with reservations concerning the prior reports. Specifically, there was concern that this treatment had only been given at one institution and that patients had been followed for little more than 3 years. At the time this manuscript was submitted for review, one-half of the survivors (27 of 54) had been followed for more than 5 years, without an apparent decline in progression-free survival. Progression-free survival also remains excellent, despite the expansion of the treatment trial to three centers. As outlined, there is no obvious selection bias in this study, as 95% of eligible patients at the institutions were entered into the study protocol. It is impossible to directly compare survival figures between our study and other reports, but the apparent natural history of MB/PNET has not changed dramatically over the past two decades, and it seems unlikely that the high rate of survival is due to an unrecognized alteration in the natural history of the disease.[7,24] In an epidemiological study of a series of 532 medulloblastoma patients treated between 1973 and 1986, the overall 5-year survival rate was found to be 45%.[24] Reviews have recently found a trend for improving survival for patients with medulloblastoma treated in the late 1970's and early 1980's compared to patients treated 5 to 10 years earlier.[7,24] These studies concluded that the modest improvements of approximately 10% are most likely due to either the use of higher doses of radiotherapy or the addition of chemotherapy.[7,24]

Published series of patients, both from experiences at large institutes and cooperative group studies, have reported 5-year disease-free survival rates ranging between 50% and 70% in patients treated with radiotherapy alone since 1975.[4,7,8,9,11,28] The most recent Children's Cancer Group (CCG) prospective, randomized cooperative trial for children with either disseminated, partially resected, or focally extensive disease compared outcome after treatment with pre- and postradiotherapy chemotherapy combined with therapy consisting of eight drugs in 1 day to outcome for patients treated with radiotherapy and adjuvant CCNU and vincristine.[30] This study, utilizing entry criteria similar to those employed in our study, demonstrated an overall 5-year progression-free survival rate of 57%. A randomized cooperative group trial recently completed by the CCG and the Pediatric Oncology Group (POG) for children older than 3 years of age, diagnosed between 1986 and 1990 with nondisseminated, totally resected medulloblastoma treated with radiotherapy alone demonstrated a 3-year, disease-free survival rate of nearly 80%, but a 5-year survival rate of less than 70%.[3] Most of these patients (who were considered to have "good-risk" disease) would not have been eligible for our study because of their favorable risk factors at diagnosis. It is of interest that patients in our study with overall less favorable risk factors survived at a relatively equal or possibly better rate than those children with "good-risk" factors treated with radiotherapy alone.

Impact of Risk Factors

When our present study was begun in 1983, the available information suggested that patients with posterior fossa MB/PNET had different prognoses depending upon the size of the original tumor at the time of diagnosis, invasion of the tumor into the brain stem, and extent of dissemination.[1,4,13,22] Results of the CCG and the International Society of Pediatric Oncology randomized trials suggested that patients with larger primary tumors, those that invaded the brain stem or that had metastasized at the time of diagnosis, had a poorer prognosis and were more likely to benefit from the addition of chemotherapy.[1,4,20,28] For these reasons, treatment with chemotherapy was ini-

tially limited to patients with these characteristics when this study began. The selection criteria initially used in our study were more stringent than those employed by the CCG for their poor-risk study, as children with totally resected T_3 and T_4 tumors were ineligible for entry in our study, but were eligible for entry in the CCG radiotherapy plus adjuvant chemotherapy trial. Over the past 10 years, information primarily derived from the prospective CCG adjuvant eight-drugs-in-1-day therapy versus adjuvant CCNU and vincristine trial has suggested that the extent of local disease at the time of diagnosis is not a predictor of outcome, if all patients are treated with chemotherapy.[30] In addition, the significance of brainstem involvement at the time of diagnosis is now being questioned, because in the most recent CCG trial in which all patients received chemotherapy, the presence of brainstem involvement did not denote a poorer outcome.[30] Only a portion of the patients treated in our study had disseminated disease (15% to 24%) at the time of diagnosis and/or subtotally resected tumors (23% to 35%). This raises the issue of what subgroup of patients with MB/PNET was actually treated in our study.

Despite the fact that this study may have treated an intermediate-risk group of children with MB/PNET, the survival figures presented compare favorably to other series reporting heterogeneous populations. For example, Jenkins, *et al*.,[11] reported a 71% 5-year survival rate for 72 children treated between 1977 and 1987 with radiation; 24 children also received postradiotherapy chemotherapy.[11] Of the patients treated in the Jenkins, *et al*., series, 24 had totally resected tumors, and disease-free survival rate was less than 50% for those with either less than total resections or dissemination at diagnosis. In a series of 65 consecutive children with posterior fossa MB/PNET treated with craniospinal radiotherapy and most with chemotherapy at the University of California, 5-year actuarial survival was 73%.[8] This series included 27 "low-risk" patients who, by our selection criteria, would not have been treated in the study. The 5-year actuarial progression-free survival rate of 85% seen in our series, even if it included 20 patients who were entered in the study due only to brainstem involvement (which in retrospect may not be a portender of poor outcome) remains encouraging.

Future Directions

The results of this study cannot be utilized to prove that all children with MB/PNET, independent of extent of resection or dissemination at the time of diagnosis, benefit from the addition of adjuvant chemotherapy. However, because the best 5-year disease-free survival rates that can be obtained from treatment with conventional doses of radiation therapy alone range between 55% and 65%, studies are indicated to explore the utility of chemotherapy for children with nondisseminated MB/PNET. Another potential application of our limited experience, as well as that of Halberg, *et al*.,[9] is to provide impetus for the study of reduced-dose craniospinal radiotherapy plus adjuvant chemotherapy to control disease in children with MB/PNET. Conventionally used doses of craniospinal radiotherapy (3600 cGy) result in well-documented intellectual and endocrinological toxicity, especially in children younger than 7 years of age at diagnosis.[19,20] Results from the recent multi-institutional cooperative group trial demonstrated that reduced-dose (2400 cGy) radiotherapy alone was inferior to conventional doses of craniospinal irradiation therapy in preventing leptomeningeal relapse.[3] A prospective randomized study comparing outcome for children with MB/PNET treated with reduced-dose radiotherapy plus chemotherapy to those receiving conventional-dose radiotherapy is needed to evaluate whether chemotherapy plus reduced-dose radiotherapy is adequate in controlling disease.

The optimum chemotherapeutic approach to be used in future trials requires study.[6] The choice of cisplatin, CCNU, and vincristine in 1983 was based on the information available at that time. The radiotherapy and adjuvant CCNU and vincristine regimen had been shown to be superior to treatment with radiotherapy alone in a randomized group trial for children with what, at that time, was defined as poor-risk MB/PNET.[4] The addition of cisplatin was based on information obtained in Phase II of the study which demonstrated that cisplatin was an active agent at the time of disease relapse in children with medulloblastoma. A Phase II trial undertaken in eight children with relapsed medulloblastoma utilizing the CCNU, vincristine, and cisplatin regimen demonstrated that it was a tolerable regimen and resulted in objective disease remission in all patients.[14,27] Since that time, other single-arm adjuvant trials have been undertaken.[18] Preirradiation chemotherapy trials utilizing drug combinations that included agents such as cisplatin, vincristine, etoposide, and cyclophosphamide have demonstrated that various drug regimens are active in children with newly diagnosed medulloblastoma.[18] However, these and other preirradiation chemotherapy trials, including one which used the eight-drugs-in-1-day approach, have yet to demonstrate any clear benefit from the utilization of chemotherapy prior to radiotherapy in any subset of children with medulloblastoma, including those with localized disease at the time of diagnosis.[18] The drug regimen utilized in the study reported here has been relatively well tolerated but over one-half of patients required cisplatin-related dosage modifications. There are obvious concerns over the ototoxicity of cisplatin; however, employing dose-modification criteria for the use of the drug, only one child required a hearing aid within the first 12 months of treatment. One potential alteration would be the substitution of carboplatin for cisplatin. However, in Phase II trials, carboplatin has not had a reproducibly high activity rate in children with recurrent medulloblastoma.[5,8] In the CCG trial, six of 14 patients with MB/PNET had an objective response to treatment, while in the POG trials, only two of 26 patients treated with carboplatin at the time of disease recurrence had a greater than 50% reduction in tumor

size. Although some of the patients treated with carboplatin had received prior cisplatin, previous cisplatin use did not fully explain the apparent borderline efficacy; as in the POG studies only one of 20 children who had not received prior cisplatin responded to carboplatin.[5] An alternative approach is to use a lesser total dose of cisplatin because most patients were able to tolerate five to six cycles of chemotherapy without significant toxicity or the need for dose modifications.

There is little information to document the efficacy of CCNU as a single agent for use in the treatment of children with medulloblastoma. *In vivo* studies utilizing medulloblastoma cell lines have suggested that cyclophosphamide is a more active alkylator agent than CCNU.[5] Cyclophosphamide can be administered intravenously and, thus, not be subject to the intrapatient variability of an oral drug such as CCNU. In addition, CCNU has been linked to long-term sequelae, especially lung toxicity.[18] However, a head-to-head trial of any other drug regimen compared to the CCNU, cisplatin, and vincristine regimen utilized in the present drug trial has never been undertaken, and no data exist to determine the potential toxicity of any other adjuvant drug regimen.

The subgroup of patients who seemed least likely to benefit from the three-drug adjuvant chemotherapy utilized in this trial were those patients with disseminated disease at the time of diagnosis. Throughout the period of study, 15 patients had disseminated disease at the time of diagnosis and the actuarial 5-year progression-free survival rate for this group of patients was 67% ± 15%. This overall survival rate is quite good in comparison to other reported medulloblastoma studies, but there is room for improvement, perhaps by intensifying therapy. Such an intensification would probably require the delivery of preirradiation chemotherapy, because a more aggressive chemotherapeutic regimen would be difficult to deliver after craniospinal irradiation.

Finally, a disturbing factor is the development, to date, of a second malignancy in three patients participating in the trial. Both chemotherapy and radiotherapy have been associated with a second malignancy.[29] Dose-response relationships have been demonstrated for both and when alkylating-agents chemotherapy and radiotherapy are used in combination, there is synergy with regard to a second malignancy. Alkylating agents have been primarily associated with rapidly fatal acute leukemias.[17] The bifunctional alkylating agent CCNU and the nitrosoureas are probable human carcinogens because of demonstrated carcinogenicity in animals; they are also known mutagens in animals and humans.[10,17] Similarly, cisplatin is a mutagen and is probably carcinogenic. Vincristine is likewise a mutagen, but has not been classified as a carcinogen in mice or humans.[10] Detailed follow-up studies are required to ascertain whether this drug combination or others will be associated with an increased risk of a second malignancy, as compared to their occurrence after radiotherapy alone in children with medulloblastoma, and whether such a risk will offset the possible benefits of treatment with adjuvant chemotherapy.

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