Treatment strategies for medulloblastoma and primitive neuroectodermal tumors

Deborah R. Gold, M.D., Roger J. Packer, M.D., and Bruce H. Cohen, M.D.

Departments of Neurology and Neurosurgery, and The Brain Tumor Center, The Cleveland Clinic Foundation, Cleveland, Ohio; and Division of Neurology and Pediatrics, Children's National Medical Center, George Washington University, Washington, DC

Medulloblastoma and primitive neuroectodermal tumors (PNETs) are the most common malignant brain tumors in children. The concern for late sequelae of neuraxis irradiation and the obligation to improve disease-free survival in children who harbor malignant brain tumors has led to the additional provision of systemic chemotherapy to standard- and reduced-dose radiotherapy, as well as to the evaluation of alternate modes of radiotherapy delivery. Analysis of evidence has suggested that chemotherapy has an impact on length of survival in children with medulloblastoma and PNETs. The question remains as to whether chemotherapy combined with reduced-dose radiotherapy provides greater benefit than standard-dose radiotherapy alone, and which subset of children the treatment most benefits. Also unanswered is the question of whether chemotherapy can serve as the primary treatment in infants with these lesions. In an attempt to help answer these questions, the authors review the major chemotherapy and radiotherapy trials for newly diagnosed patients and those with recurrent medulloblastoma and PNETs.

Key Words * medulloblastoma * primitive neuroectodermal tumor * radiotherapy * chemotherapy

Tumors of the central nervous system (CNS) are the most common malignancy of childhood, comprising approximately 20% of all childhood malignancies.[55] Medulloblastoma accounts for 30% and supratentorial primitive neuroectodermal tumors (PNETs) for 1 to 2% of all childhood brain tumors.[8,33]

Bailey and Cushing[7] first used the term "medulloblastoma" in 1925 to describe a pluripotential embryonal tumor that arose in the cerebellum. The term "PNET" was proposed by Hart and Earle[38] in 1973 as a nonspecific designation to include medulloblastoma and similarly appearing CNS neoplasms. Controversy remains with respect to nomenclature. Histopathologically, both the medulloblastoma and PNETs are composed of small, round, poorly differentiated cells with sparse cytoplasm, and hyperchromatic nuclei. These tumors may differentiate along neuronal, glial, ependymal, or photoreceptor pathways. For the purpose of this paper, the term medulloblastoma will be used to signify those PNETs that originate in the posterior fossa, whereas the term PNET will be used as a general term to describe these tumors without regard to location. A worse prognosis exists in those patients with tumors that express glial fibrillary acidic protein (GFAP). In a group of 98 patients with PNETs, the expression of GFAP correlated with a 6.7-fold increased risk of recurrence compared with GFAP-negative tumors. In addition, high expression of GFAP was found to have further prognostic value (threefold greater risk of recurrence compared with low GFAP; $p = 0.0197$). Finally, the presence of other proteins (neurofilament or photoreceptor) was not found to be of prognostic value.[41] Other measures of tumor aggressiveness, such as the degree of tumor cell apoptosis and/or cytogenetic features (that is, chromosome 17 deletions) have been shown to have varying degrees of utility with regard to predicting survival.[24,40]

Cerebrospinal fluid (CSF) dissemination early in the course of disease is common, especially in younger children. In cases of medulloblastoma, the local extent of tumor and degree of metastatic spread is based on the Chang staging criteria (Table 1).[11] Because of the tumor's metastatic tendency, curative excision is rarely possible, and, historically, surgical resection has been followed by neuraxis radiation, which considerably lessens the risk of dissemination beyond the primary tumor site.

TABLE 1 CLASSIFICATION OF MEDULLOBLASTOMA*	
T stage	
T ₁	tumor < 3 cm diameter, limited to classic midline position in vermis, roof of 4th ventricle or, less frequently, to cerebellar hemispheres
T ₂	tumor > 3 cm, invading 1 adjacent structure or partially filling 4th ventricle
T _{3a}	tumor further invading 2 adjacent structures or completely filling 4th ventricle w/ extension into Sylvian aqueduct, Magendie's foramen, or foramen of Luschka, producing marked hydrocephalus
T _{3b}	tumor arising from floor of, and filling, 4th ventricle
T ₄	tumor spread through Sylvian aqueduct to involve 3rd ventricle, mid brain, or down into upper cervical cord
M stage	
M ₀	no gross subarachnoid or hematogenous metastasis
M ₁	microscopic tumor cells in CSF
M ₂	gross nodular seeding in cerebellum, cerebral subarachnoid space, or in 3rd or 4th ventricle
M ₃	gross nodular seeding in spinal subarachnoid space
M ₄	extraneural metastasis
* This classification system was devised by Chang and colleagues.	

Survival in patients with medulloblastoma/PNET has improved over the past several decades. This can be attributed to advances in earlier diagnosis, anesthesia, surgical techniques, and improved delivery of craniospinal radiation. In addition, the provision of chemotherapy, which was previously thought of as an adjuvant to the standard treatments of surgery and radiotherapy, has resulted in improved progression-free survival (PFS) rates in children with medulloblastoma. The addition of cytotoxic agents has become part of the standard approach in the treatment of disseminated, high-grade and -stage PNETs as well as in an effort to delay, or even avoid, radiotherapy in young children.

With the potential for increased duration of disease-free survival, the long-standing concern with regard to the late postirradiation sequelae of the craniospinal region (that is, neurocognitive delay, growth failure, endocrinopathies, and second malignancies) becomes an important factor in treatment decision making. The individual fraction size and total dose of neuraxis radiation appear to be important factors in disease control as well as initiation of side effects. The use of hyperfractionated radiotherapy has been investigated in recent years in an effort to increase the tolerated dose of radiation without diminishing the antitumor effect. The effectiveness of reduced-dose craniospinal radiotherapy and the duration over which this therapy is delivered have also been examined.

In large multicenter trials in which adjuvant chemotherapy in patients with newly diagnosed PNET has been investigated, 5-year survival figures ranging from 40 to 75% have been reported.[25,56] Over the past two decades, stratification of children into standard- and high-risk categories has become increasingly important when taking into account the planning of treatment strategies and evaluating outcome measures. In practice, however, the definitions of these risk groups have been quite variable. Packer, et al.,[47] have defined standard-risk disease as that in which the following criteria are met: more than 4 years of age at diagnosis, gross-total resection or near-total resection, and no dissemination (M_0); high-risk features include less than 4 years of age at diagnosis and/or subtotal resection and/or evidence of dissemination (M_{1-4}). Investigators disagree as to the importance of minimal residual tumor, as a single variable, on survival.[2]

In this review we will present data from the major chemotherapy and radiotherapy trials for newly diagnosed patients and/or those with recurrent medulloblastoma and PNETs. We will discuss evidence for the use of specific chemotherapeutic agents, trends in modes of radiotherapy administration, and the use of autologous stem cell rescue (SCR). Although it is not conventional to refer to clinical trials by a proprietary name, for the benefit of readability, we will use recognized study names where possible.

SURGICAL MANAGEMENT OF MEDULLOBLASTOMA AND PNETS

Resection of the primary tumor is an essential component in the initial management of children with PNET, both for diagnostic and therapeutic purposes. The influence of the extent of surgical resection on survival outcome remains controversial. It is generally accepted that survival is worse for patients with medulloblastoma in whom biopsy samples alone are obtained compared with the duration of survival in patients in whom more complete resections are performed.[15,47] Evans, et al.,[25] have reported that the extent of surgical resection had no effect on the duration of survival in their cases while controlling for other prognostic factors. In another series of children with medulloblastoma, resection alone did not correlate with outcome in children with Stage M_0 tumors were older than 3 years of age. Prognosis was considerably improved if there was less than 1.5 cm² of residual tumor following surgery (5-year PFS of 77% compared with 53% if > 1.5 cm² residual tumor; p = 0.033).[2] Overall, the goal in surgical management is to attempt gross-total resection when feasible, without creating further neurological harm to the child.[13]

Because the supratentorial PNET (SPNET) is rare, information concerning the effect of surgical resection is more limited. In a study of 52 children with SPNET, no significant difference in survival was found when comparing varying degrees of surgical excision (as reported by neurosurgeons' estimates of extent of tumor removal). In children with less than 1.5 cm² of residual disease, a 4-year survival rate of 40% was demonstrated compared with 13% in children with more than 1.5 cm², although this difference was not statistically significant (p = 0.19), potentially because of small patient numbers.[1,14]

RADIOTHERAPY TRIALS IN MEDULLOBLASTOMA/PNET

Reduced- and Standard-Dose Neuraxis Radiation

Table 2 provides a summary of the results obtained in various radiotherapy trials.

TABLE 2
SUMMARY OF DATA OBTAINED IN RADIOTHERAPY TRIALS REPORTED IN THE LITERATURE*

Authors & Year	Tumor Type (no.), Stage	Hyperfractionated RT	RT Dose (cGy)	Chemotherapy			Survival		
				Pre-RT Induction	During RT	Post-RT Consolidation	Overall	High Risk	Standard Stage
Allen, et al., 1996	MB (15), T _{3b} +M ₀	yes	PF: 3600, CSA: 3600,	none	none	cisplatin 20 mg/m ² IV etoposide 50 mg/m ² IV		5/7 PD or RD	6.5-yr PFS 95%
	MB (4), T _{3b} +M ₂₋₃		PF: 3600, CSA: 3600,	none	none	CPM 900 mg/m ² IV VCR 1.5 mg/m ² IV			
	PNET (4): M ₀ (1) M ₃ (3)		PF: 3600, CSA: 3600, (boost: 4400–5600 if spinal metastases)	none	none	CBP 150 mg/m ² IV VCR 1.5 mg/m ² IV			
Deutsch, et al., 1996	MB (63), T _{1-3a} /M ₀		PF: 5400, CSA: 3600 / 20 fx	none	none	none		N/A	7.9% re-lapsed, 3-yr local control 80†
	MB (60), T _{1-3a} /M ₀		PF: 5400, CSA: 2340 / 13 fx						28.3% re-lapsed, 3-yr local control 56%†
Marymont, et al., 1996	MB (2), SPNET (1), all stages	yes	PF: 3360, CSA: 3120,		none		3-yr PFS 48%		64% never recurred
	MB (7), SPNET (1), all stages		PF: 3800, CSA: 3400		none	8-in-1			
	MB (2), high risk (M ₃)		PF: 3400, CSA: 2600,	unspecified agents failed	none			no survivors	
Del Charco, et al., 1998	MB (53), all stages		PF: 3430–6960, CSA: 2330–4560 (boost: 3780–6480 if spinal metastases)	yes (4)	yes (1)	yes (11)	5-yr sur 68%; 10-yr sur 64%, 5-yr PFS 61%, 10-yr PFS 52%	if chemo: 5-yr PFS 75%; 5-yr PFS 90%† If no chemo: 5-yr PFS 43%; 5-yr PFS 50%†	
Prados, et al., 1999	MB/PNET (19), standard risk	yes	PF or supra primary: 7200, CSA: 3000 spinal cord primary: 5600, CSA: 3000	none	none	none			3-yr 79%, 3-yr PFS 63%, (MB 5-yr 69%, 5-yr PFS 49%)
	MB/PNET/PB (20) high risk				none	CCNU 75 mg/m ² cisplatin 75 mg/m ² VCR 1.4 mg/m ²		3-yr 70%; 3-yr PFS 60%, (MB 3-yr PFS 56%)	

* CBP = carboplatin; chemo = chemotherapy; CPM = cyclophosphamide; CSA = craniospinal neuraxis; fx=fractions; NA= not applicable; PB= pineoblastoma; PD = progressive disease; PF = posterior fossa; PFS=progression-free survival; RD = reduced disease; RT = radiotherapy; supra = supratentorial; sur = survival; VCR = vincristine.
† p = 0.01.
‡ p = 0.0025.

The medulloblastoma/PNETs tend to invade adjacent structures and to metastasize through CSF pathways. This pattern of dissemination has led to the approach of directing the radiation dose at the entire craniospinal axis, even in patients who present at initial diagnosis without clinical or radiological evidence of tumor spread. Craniospinal radiotherapy has been an essential component of the treatment of medulloblastoma since it was first introduced as an additional postoperative therapy in the 1950s. Standard radiotherapy involves delivering radiation to the craniospinal axis in a dose of 3000 to 3500 cGy followed by a total boost of 5000 to 5500 cGy to the primary tumor region. Radiotherapy is typically provided over a 6 to 7-week period. Long-term sequelae of this treatment include neurocognitive delay, growth failure, endocrinopathy, and secondary oncogenesis. Because some long-term effects are more severe in younger children, attempts at reducing the radiation dose by 15 to 25% have been made in children under 10 years of age, or even delaying the start of radiotherapy.[17,18,45,52] The minimum effective dose to achieve optimum disease control is not yet known.

In a retrospective review of the literature, analysis of the data suggested that a radiation dose of less than 5000 cGy delivered to the posterior fossa was associated with worse outcome, regardless of patient age.[52] Five-year survival rates, corrected for the number of patients in each of 12 studies, were 35% for patients in whom a less than 5000 cGy dose was given compared with 66% for those receiving a greater than 5000 cGy dose delivered to the primary tumor region.[52] In a study conducted by the International Society of Pediatric Oncology and the (German) Society of Paediatric Oncology (SIOP II), patients with low-risk medulloblastoma were randomized to receive or not receive chemotherapy as well as randomized to reduced- or standard-dose neuraxis radiotherapy treatment groups. In those patients receiving a reduced craniospinal axis dose of 2500 cGy, a worse mean survival rate was found when compared with those treated with a dose of 3500 cGy (5-year event-free survival [EFS] 55.3% and 67.6 respectively; p = 0.07). Interestingly, in a subgroup analysis, the addition of a chemotherapy regimen produced a negative effect on survival in patients who received reduced doses of craniospinal axis radiation (p = 0.0049).[6]

In a collaborative effort between Children's Cancer Group and Pediatric Oncology Group, standard-risk patients (in whom the following criteria

were met: M₀ stage tumor, at least subtotal resection, and no brainstem involvement) were randomized to receive standard dose of craniospinal axis radiation (3,600 cGy in 20 fractions) or reduced dose (2,340 cGy in 13 fractions). A posterior fossa boost of 5400 cGy was given in both treatment groups. The study was closed before patient accrual was complete because of an increased number of recurrences in the low-dose treatment group (31% compared with 15% recurrence, respectively, at 16 months).[16]

Hyperfractionated Radiation

Radiation-dose intensification may improve outcome in high-risk patients with medulloblastoma/PNET. Hyperfractionated radiotherapy allows the delivery of higher doses of radiation with the goal of improved tumor control without increased toxicity. Table 2 provides a summary of radiotherapy trials, in several of which hyperfractionated radiotherapy was used. Hyperfractionated radiotherapy is based on the hypothesis that normal brain tissue is more effective at repairing sublethal radiation-induced damage than tumor tissue. More frequent small-dose fractions of radiation increase the chance of injuring proliferating neoplastic tissue and reducing tumor cell repopulation, while sparing noninvolved brain. The typical hyperfractionated radiotherapy schedule consists of twice-daily fraction sizes of 100 to 120 cGy to a total (increased) dose of 7200 to 7800 cGy. In earlier studies in which the authors investigated the use of hyperfractionation in the treatment of brainstem gliomas in children the feasibility of this treatment was documented.[28,29,46] In a later report on 119 patients treated with 7200 to 7800 cGy hyperfractionated radiotherapy no survival advantage was shown for those patients harboring typical diffuse brainstem gliomas, but it did confirm the feasibility of this technique, which could be applied to other tumor models.[42]

The use of hyperfractionated radiotherapy for treatment of medulloblastoma and PNETs has only recently been investigated. In one trial, 13 patients (median age 7 years) were prospectively assigned to undergo hyperfractionated radiotherapy in various total doses, depending on extent of residual disease. Doses ranged from 6400 to 7200 cGy, given in twice-daily fractions of 100 cGy or 120 cGy. Adjuvant chemotherapy was undertaken in those patients with leptomeningeal spread. Collectively, the median PFS was 32 months, with a 3-year PFS rate of 48%. The primary source of treatment failure was local tumor recurrence. Given that in 12 of 13 of these patients there were poor-risk features, the results were promising. The results of this study suggested the need for a randomized trial in which conventional radiotherapy is compared with hyperfractionated radiotherapy.[44]

Allen, et al.,[3] have evaluated hyperfractionated radiotherapy followed by multiagent chemotherapy in 23 children in whom medulloblastoma/PNETs had been newly diagnosed. The total dose of hyperfractionated radiotherapy was 7200 cGy, given in twice-daily fractions of 100 cGy. Of 19 patients with medulloblastoma, 15 were considered to be at standard risk (M₀ stage). Fourteen (93%) of 15 of these children were in continuous remission at a median of 75 months. Of the seven children with high M-stage tumors, the death of five patients with progressive or recurrent disease suggests that there is a need for alternative treatment regimens in these high-risk patients.

In a more recent study of hyperfractionated radiotherapy in combination with adjuvant chemotherapy in patients with high-risk, newly diagnosed medulloblastoma/PNET and malignant ependymoma, 3-year survival rates of 70% in poor-risk patients and 79% in standard-risk patients were demonstrated.[50] When the data for patients with medulloblastoma are evaluated separately, the 5-year survival rate was 69% in standard-risk patients, with failure outside the primary site occurring in 43% of patients; these results were not significantly different when compared with those obtained in previous studies of single-fraction radiotherapy. Finally, overall survival and PFS rates in high-risk patients were similar to those obtained in the standard-risk group in this study. Whether the results were influenced by the addition of hyperfractionated radiotherapy or adjuvant chemotherapy is unclear and warrants additional research.[50]

Chemotherapy Trials

Over the past two decades, the treatment of medulloblastoma/PNETs has evolved to include chemotherapy as part of the current standard for higher-risk patients. These tumors are susceptible to cytotoxic agents because of their prominent vascularity, high growth fraction, and biologically inherent chemosensitivity. Investigators have developed human CNS tumor-derived cell lines and xenografts to better distinguish between clinically active agents against this neoplasm. Current in vitro and in vivo models of human medulloblastoma have allowed for therapeutic analyses of various agents prior to their use in humans.[54] Subsequent clinical phase II and III trials can then be conducted in which drugs with demonstrated in vitro sensitivity are used.[31,32]

To date, a number of agents have been shown to be effective in the treatment of newly diagnosed and recurrent medulloblastoma/PNETs. Their efficacy has been defined based on objective response (that is, the reduction in tumor size or lack of progression) and, in recent years, on improvement in survival rates. In a single-institution retrospective analysis, Packer, et al.,[49] compared survival data obtained in children who underwent craniospinal radiotherapy alone (from 1975-1983) and radiotherapy followed by adjuvant chemotherapy in which CCNU, cisplatin, and vincristine were administered in poor-risk patients (from 1983-1989). There was no significant difference in survival rates among standard-risk patients; however, there was a significant survival advantage in those poor-risk children who underwent adjuvant chemotherapy (87%) compared with those who did not (33%). Although this was not a randomized study (aside from the incorporation of chemotherapy), surgical techniques, staging, and treatment were similar during the two time periods, which indicates the effectiveness of adjuvant chemotherapy.[49]

Newly Diagnosed Medulloblastoma and PNETs

Nonrandomized Trials. Table 3 provides a summary of nonrandomized chemotherapy trials. As discussed in the previous section, in a single-institution trial, Packer, et al.,[49] demonstrated that chemotherapy with cisplatin, CCNU, and vincristine, in combination with radiotherapy, benefited children with high-risk medulloblastoma. In an effort to determine if this regimen provided improved survival, the trial was extended over 10 years, and additional institutions became involved.[48] Sixty-three children with high-risk medulloblastoma (defined by the presence of postoperative tumor and/or greater than M₀ stage tumor), were treated with vincristine weekly during radiotherapy (2400-3600 cGy [craniospinal axis], 5400 cGy [local]) followed by up to eight 6-week cycles of cisplatin, CCNU, and vincristine. The overall 5-year PFS rate of 85 ± 6% confirms the advantage previously noted with this regimen. In patients in whom there was evidence of dissemination of the disease at the time of diagnosis, a 5-year PFS rate of 67 ± 15% was reported (compared with 90 ± 6% in patients without metastatic disease; p = 0.037).[46] During the

same era, Goldwein, et al.,[36] reported the results of treating children under the age of 5 years with reduced-dose (1800-cGy) craniospinal radiation therapy and adjuvant vincristine, CCNU, and vincristine chemotherapy. The 4-year PFS rate was 69%, and the overall survival rate at 6 years was 70 ± 20%.[36] Prospective neuropsychological testing conducted pre- and postirradiation showed that the mean intelligence quotient score in six of the 10 patients did not change, indicating benefit to reduced-dose radiotherapy.[35]

TABLE 3 SUMMARY OF DATA OBTAINED IN NONRANDOMIZED CHEMOTHERAPY TRIALS REPORTED IN THE LITERATURE*								
Authors & Year	Tumor Type (no.), Stage	RT Dose (cGy)	Chemotherapy			Survival		
			Pre-RT Induction	During RT	Post-RT Consolidation	Overall	High Risk	Standard Stage
Duffner, et al., 1993	MB (53)	PF: 5400 (5000†), CSA: 3520 (2400†)	CPM (65 mg/kg) IV VCR (.65 mg/kg) IV cisplatin (4 mg/kg) IV etoposide (6.5 mg/kg) IV same as above	none	none		2-yr sur 46 ± 7% 2-yr PFS 34 ± 8%	
	SPNET (30)	primary: 5400 (5000†) CSA: 3520 (2400†)	same as above	none	none		2-yr sur 21 ± 7% 2-yr PFS 19 ± 12% 3-yr PFS 90 ± 4%, 5-yr PFS 85 ± 6%	NA
Packer, et al., 1994	MB (63), high risk	primary: 1800–1980, CSA: 3600 2400 if < 5y	none	VCR 1.5 mg/m ²	VCR 1.5 mg/m ² CCNU 75 mg/m ² CDDP 68 mg/m ²	87.3% free of progressive disease 7-yr PFS 59 + 13%		
Gentet, et al., 1995	MB (31), standard risk	PF: 5000–5500 CSA: 3000–3600, WB: 2700	8-in-1 MTX 12 g/m ² leucovorin					7-yr PFS 62 ± 21%
	MB (37), high risk	PF: 5000–5500 CSA: 3000–3600, WB: 2700		8-in-1 MTX 12g/m ² leucovorin	8-in-1	age < 2 yrs: 7-yr PFS 55% (vs 58% if > 2 yrs), NB: not significant median TTP 11 mos 6-yr sur 70 ± 20% 6-yr relapse-free 70%	7-yr PFS 57 ± 16% NSD	
Goldwein, et al., 1996	MB (10)	PF: 5040–5580, CSA: 1800	none	VCR	VCR CDDP CCNU			
Prados, et al., 1996	MB (27), PB (5), SPNET (2)	primary: 5400, CSA: 2400 (boost: 1500–1600 if spinal metastases)	6TG 30 mg/m ² po PCB 50 mg/m ² po DBD 400 mg/m ² po CCNU 110 mg/m ² po VCR 1.4 mg/m ² IV	hydroxyurea	6TG 30 mg/m ² po PCB 50 mg/m ² po DBD 400 mg/m ² po CCNU 110 mg/m ² po VCR 1.4 mg/m ² IV	5-yr PFS 35% 5-yr sur 56% (MB 5-yr PFS 36%, 5-yr sur 56%)	5-yr PFS 21%, 5-yr sur 42%, (MB 5-yr PFS 20%, 5-yr sur 40%)	5-yr PFS 52%, 5-yr sur 71%, (MB 5-yr PFS 52%, 5-yr sur 73%)
Sawamura, et al., 1996	MB (10)	if age 2–5 yrs primary: 3000–3200, CSA: 1800; if age > 6 yrs primary: 3000, CSA: 2400	ifosfamide 900 mg/m ² cisplatin 20 mg/m ² etoposide 60 mg/m ²	none	ifosfamide 900 mg/m ² cisplatin 20 mg/m ² etoposide 60 mg/m ²	2-yr DFS 70%		
Bergman, et al., 1997	MB (25) standard risk	if age 3–5 yrs: PF: 3000, CSA: 2400, if age > 6 yrs PF: 1800, CSA: 3600	none	VCR 1.5 mg/ m ² IV	CBP 560 mg/m ² VCR 1.5 mg/m ²		NA	3-yr PFS 73 ± 9%
Hartsell, et al., 1997	MB (23) < 3 yrs	schedule, dose & fractions varied based on protocol	prolonged multiagent			5-yr sur 60%, 5-yr EFS 37%	5-yr sur 58%, 5-yr EFS 26%	NA
	MB (30) > 3 yrs, T ₃₀ and/or M ₁₊		agents varied				5-yr sur 61%, 5-yr EFS 44%	

* DB = dibromodulcitol; DFS = disease-free survival; MTX = methotrexate; NSD = no significant difference; PCB = procarbazine; pdn = prednisone; WB = whole brain; 6TG = 6-thioguanine.

The M7 French Cooperative Study[34] was designed to evaluate the "eight-drugs-in-1-day (8-in-1) chemotherapy regimen and radiotherapy. In standard-risk patients who received two courses of the 8-in-1 regimen and methotrexate, followed by radiotherapy (5000–5500 cGy [posterior fossa] and 3000–3600 cGy [craniospinal axis]), their 7-year PFS rate was 62 ± 21%. In high-risk patients who were treated with four additional courses of the 8-in-1 chemotherapy regimen after undergoing craniospinal radiotherapy, a 7-year PFS rate of 57 ± 16% was demonstrated. There was no significant difference in survival between these two groups (p = 0.26). In contrast to the data in many previously published reports, patient age, extent of resection, and radiotherapy dose were not found to have any prognostic value.[34]

In a single-arm, phase II trial, Prados, et al.,[51] have studied the toxicity and PFS rates in patients in whom medulloblastoma/PNET have been newly diagnosed and who have undergone reduced-dose craniospinal radiotherapy (2400 cGy [craniospinal axis] 5400 cGy [local]) and adjuvant chemotherapy. Patients received one cycle of chemotherapy (procarbazine, 6-thioguanine, dibromodulcitol, CCNU and vincristine) pre- and six cycles postirradiation. The 5-year PFS and 5-year survival in patients with stage M_{1–4} disease was only 21% and 42%, respectively, which are significantly lower than the rates reported earlier.[6,25,48,56] The authors postulated that the reason for this inferior result was related to the lowered craniospinal radiation dose and/or the absence of cisplatin in this chemotherapy regimen.[51]

Of interest, in a pilot study conducted in Japan, where survival rates for patients with medulloblastoma are worse than those in the United States, 10 children with newly diagnosed medulloblastoma were treated with ifosfamide, cisplatin, and etoposide after undergoing either reduced- or standard-dose radiotherapy depending on age at time of treatment. The 2-year disease-free survival rate was 70%, which suggests that this regimen is feasible for treatment of patients with medulloblastoma, although further evaluation is necessary to clarify long-term data and to compare critically this regimen with others known to be efficacious.[53]

Hartsell, et al.,[39] have studied whether a variety of chemotherapeutic agents administered prior to radiotherapy affected time to disease recurrence and patterns of treatment failure in patients harboring medulloblastoma. Children younger than 3 years of age underwent a prolonged period of chemotherapy (the agents varied depending on protocol) in an attempt to delay the need for craniospinal radiation. Older patients, or those with

more advanced disease (stage T_{3b-4} or M₁₋₄ stage disease, or postoperative residual tumor), underwent chemotherapy followed by radiotherapy. The 5-year survival rate was 58% in the younger group and 61% in those in the older group. Seventeen of 23 children less than 3 years of age experienced disease progression while undergoing chemotherapy; the most common site of progression was the primary tumor site. These children subsequently underwent radiotherapy, and seven of 17 were free of disease at a median of 62 months. In the older group, the disease progressed in 10 of 30 patients during chemotherapy (posterior fossa in four and neuraxis in six). In the 20 children in whom disease did not progress, 15 remained free of disease after craniospinal radiotherapy. Their data suggested that in patients with M₀ stage disease at diagnosis, the risk of CSF progression increases with duration of chemotherapy, which indicated that the effects of delaying radiotherapy may be detrimental in these standard-risk patients.[39]

In an effort to address the long-term effects of radiotherapy in young children and in an attempt to improve survival in what is considered the poorest-risk group, the Pediatric Oncology Group initiated a pilot study of 198 patients. Chemotherapy was used in lieu of radiotherapy until the children were 3 years of age, at which time they were to receive craniospinal radiation treatment. The patients received two alternating cycles of cyclophosphamide and vincristine followed by a cycle of cisplatin and etoposide, which were repeated in this sequence for 2 years if the patient had been younger than age 24 months at diagnosis; for 1 year if between age 24 and 36 months at diagnosis; or until disease progression was evident. Craniospinal radiotherapy was to be provided after chemotherapy. The overall 2-year PFS rate was 34 ± 8% in patients with medulloblastoma and 19 ± 12% in those with SPNET. Children in whom disease was localized and in whom a gross-total resection was performed fared the best (PFS rate of 74% at 1 year in children less than 24 months of age and PFS rate of 91% at 2 years in those between 24-36 months of age). The results were also encouraging in those children in whom residual disease was demonstrated following surgery (estimated 2-year PFS rate of 92%), even in the presence of metastases. In addition, in patients who were without residual disease following chemotherapy, reduced neuraxis radiation (2400 cGy) produced results equivalent to those in older children with similar staged disease treated with standard-dose radiotherapy. Finally, in 27 children who underwent neurodevelopmental evaluations prior to chemotherapy and at one year posttherapy, there was no significant decline in neurocognitive function.[17] In a subsequent analysis of the 75 surviving children at a median survival time of 6.4 years, five had developed second malignancies, with an actuarial risk of 11.3% at 8 years. These malignancies, including sarcoma (two cases), myelodysplastic syndrome, acute myelogenous leukemia, and meningioma, occurred in both children who did and did not undergo radiotherapy.[20]

In a multiinstitutional study, undertaken by the Australian and New Zealand Children's Cancer Study Group (Baby Brain '91), the use of a VETOPEC-based (vincristine, etoposide, and cyclophosphamide) regimen was used in children less than 4 years of age. Postoperative chemotherapy was administered to postpone the delivery of radiation. In 12 evaluable patients with medulloblastoma, the combined complete and partial response rate was 82%, and in the six patients with SPNET it was 50%. Median survival for patients with medulloblastoma was 25 months, and in those with SPNET it was 48 months.[59]

High-dose chemotherapy followed by either autologous bone marrow rescue (BMR) or autologous SCR has been performed in young children with medulloblastoma/PNET. In one study, children first received five cycles of conventional chemotherapeutic agents (vincristine, cisplatin, cyclophosphamide, and etoposide). In those children who responded to this initial treatment (complete response or tumor reduction amenable to surgical resection), high-dose chemotherapy with autologous SCR was initiated. No patients received radiotherapy during the time of this study. In 13 patients under the age of 3 years with newly diagnosed medulloblastoma, a 25-month EFS rate of 37.8% and an overall survival rate of 66% were achieved.[22]

Randomized Trials. Several prospective, cooperative group studies have been conducted in an attempt to determine if the addition of chemotherapy to radiotherapy leads to an increase in survival rates in children with medulloblastoma/PNET (Table 4). In one such randomized phase III study (CCSG-942)[25] the authors compared standard radiotherapy with or without the addition of vincristine, CCNU, and prednisone in patients with newly diagnosed medulloblastoma/PNET. Overall, there was no significant difference in EFS rates between the radiotherapy group (52%) compared with the combined radiotherapy/chemotherapy group (57%). Despite this, in the subset of children with extensive disease (stage M₁₋₃ or T₃₋₄), the 5-year EFS rate was improved in the group undergoing chemotherapy (46% compared with 0% respectively; p = 0.006).[25]

TABLE 4
SUMMARY OF DATA OBTAINED IN RANDOMIZED CHEMOTHERAPY TRIALS REPORTED IN THE LITERATURE

Authors & Year (trial)	Type of Tumor (no.), Stage	RT Dose (cGy)	Pre-RT Induction	Chemotherapy		Survival		
				During RT	Post-RT/ Consolidation	Overall	High Risk	Standard Stage
Evans, et al., 1990 (CCSG-942)	MB (88), T ₁₋₂ , M ₀₋₃	PF: 5000–5500 CSA: 3500–4000 (boost: to 5000 if spinal me- tastases)	none	VCR 1.5 mg/m ²	VCR 1.5 mg/m ² IV CCNU 100 mg/m ² po Pdn 40 mg/m ² po	5-yr sur 64% 5-yr EFS 57%	5-yr EFS 46%†	5-yr EFS 65%
	MB (91), T ₃₋₄ , M ₀₋₃	PF: 5000–5500, CSA: 3500–4000 (boost: to 5000 if spinal me- tastases)	none	none	none	5-yr sur 68% 5-yr EFS 52% NSD	5-yr EFS 0%†	5-yr EFS 62%
Bailey, et al., 1995 (SICOP II)	MB (40) standard risk	PF: 2000, CSA: 3500	none	none	none			5-yr EFS 60 ± 7.8% §
	MB (36) standard risk	PF: 3000, CSA: 2500	none	none	none			5-yr EFS 69.1 ± 7.8% §
	MB (38) standard risk	PF: 2000, CSA: 3500	PCB 1.5 mg/m ² VCR 100 mg/m ² MTX 2 g/m ² leucovorin Pdn 100 mg/m ²	none	none	5-yr EFS 58.9% (if chemo: 59.8 ± 3.7%; if none, 57.9 ± 3.8%) NSD		EFS 75.3 ± 7.2% §
	MB (36), standard risk	PF: 3000, CSA: 2500	same as above	none	none			5-yr EFS 41.7 ± 8.2% §
	MB (62)	PF: 2000, CSA: 3500	same as above	none	none		5-yr EFS 56 ± 6.5%	
Cohen, et al., 1995	MB (71), high risk	PF: 2000, CSA: 3500	none	none	none			5-yr EFS 52.8 ± 6.1% NSD
	SPNET (44) (includes 17 PB)	3600	none	VCR 1.5 mg/m ²	VCR 1.5 mg/m ² CCNU 100 mg/m ² Pdn 40 mg/m ²	3-yr PFS 35 ± 12%		
Zeltzer, et al., 1999 (CCG-921)		3600	8-in-1 (2 cycles)	none	8-in-1	3-yr PFS 52 ± 8% (PB 3-yr PFS 61 ± 13%)		
	MB (96), T _{3a+} , M ₁₊	if age < 3: primary: 5400, CSA: 3600;		VCR 1.5 mg/m ² IV CCNU 100 mg/m ² Pdn 40 mg/m ² po	7-yr sur 56 ± 5% 7-yr PFS 55 ± 5%	5-yr PFS 64 ± 5%* (M ₁ : 57 ± 10% M ₂₊ : 40 ± 8%)	5-yr PFS: M ₀ 70 ± 5% if age < 1.5, residual 78 ± 6%‡ if age > 1.5 residual 54 ± 11%‡	
	MB (92), T _{3a+} , M ₁₊	CSA: 2340 (boost: 1440–1800 if spinal metastases)	8-in-1	8-in-1		5-yr PFS 47 ± 6%*		

*p = 0.032.
†p = 0.003.
‡p = 0.023.
§p = 0.0049.

In 1986, CCG commenced a multicenter randomized trial (CCG-921)[60] in which they compared the 8-in-1 chemotherapy regimen both before and after radiotherapy; a combination of vincristine, CCNU, and prednisone (VCP) after radiotherapy was administered to patients with high-stage medulloblastoma/PNET (T_{3b-4}, M₁₋₄, and/or more than 1.5cm² of residual tumor). Chemotherapy with VCP was superior to the 8-in-1 regimen in patients with medulloblastoma, with a 5-year PFS rate of 63% compared with 45%, respectively (p = 0.006). These investigators also validated the impact of several prognostic factors on tumor progression, relapse, and/or overall patient survival. For instance, in children between the ages of 1.5 and 3 years, a 5-year PFS rate of 32% was observed when compared with 58% in children older than 3 years of age (p = 0.0014). In children over the age of 3 years, the prognostic effect of tumor dissemination was significant with regard to PFS (5-year PFS rate of 70% in patients with M₀ stage disease compared with 57% [M₁ stage] and 40% [M₂ stage]; p = 0.0006). The authors advocated the need for future clinical trials in which intensive chemotherapy is used to assess the true improvements in survival against combined VCP treatment and radiotherapy, with the current results representing the best-studied regimen to date.[60] In children with SPNET and pineoblastoma no significant difference in either survival or time to

progression between the two treatment groups was found. Despite this, the 3-year survival rate was 57% in those patients treated with adjuvant chemotherapy compared with an estimated 3-year survival rate of approximately 47% in children who underwent radiotherapy alone during the 1980s.[5,14,57,59,61]

In 1975, The International Society of Paediatric Oncology conducted a multicenter, prospective, randomized study (SIOP I) to evaluate the benefits of adjuvant chemotherapy in patients with medulloblastoma.[56] Children underwent either radiotherapy alone or radiotherapy followed by administration vincristine and CCNU. A survival advantage was found in patients undergoing chemotherapy (2-year PFS rate of 71% compared with 53% in those undergoing radiotherapy alone). This initial benefit of chemotherapy was not observed at the 5-year follow up (5-year PFS rate of 53% in both treatment arms), except for in a subgroup of patients with poor risk factors (in young children, those with brainstem involvement, and/or those with bulky residual disease), a finding similar to that seen in the Children's Cancer Study Group-942 trial undertaken by Tait, et al.,[56]. In a subsequent collaborative effort between the International Society of Paediatric Oncology and the German Society of Paediatric Oncology,[6] children were prospectively randomized to either undergo chemotherapy (with procarbazine, vincristine, methotrexate, prednisolone, and leucovorin rescue) prior to radiotherapy or to undergo radiotherapy alone (the SIOP II trial). Standard-risk patients were further randomized to undergo either reduced- or standard-dose craniospinal radiotherapy. High-risk patients received maintenance chemotherapy in which CCNU and vincristine were used (Table 3). Overall, there was no survival advantage in any of the treatment arms in which chemotherapy was used, and there was an apparent survival disadvantage when chemotherapy was used in the setting of reduced-dose radiotherapy in standard-risk patients. The authors speculated that the chemotherapy was ineffective, possibly because the dosing was less than optimal, and delayed radiotherapy was the best treatment for this disease, similar to the findings of Prados, et al.[50]

Recurrent Medulloblastoma/PNET

Local and metastatic recurrences occur in 30 to 40% of patients, with a poor prognosis for long-term survival (Table 5). As a general rule, redosing with radiotherapy is avoided because of the risk of radiation necrosis, although local radiotherapy in which stereotactic techniques are used can be applied palliatively or as part of a more comprehensive treatment. Chemotherapy options are limited by chemoresistance in those patients who have previously undergone chemotherapy. Patients may be treated with new agents in phase I and II trials or salvage attempts with high-dose chemotherapy followed by stem cell rescue.

TABLE 5 SUMMARY OF DATA OBTAINED IN CHEMOTHERAPY TRIALS FOR RECURRENT DISEASE*					
Author & Year	Tumor Type (n.o.)	Chemotherapy	Objective Response Rate	Survival	TTP
Finlay, et al., 1996	MB (9), PNET (1), PB (2)	thiotepa 300 mg/m ² etoposide 500 mg/m ² Au BMR	2 of 6	median 3.2 mos	median 3.3 mos
Dunkel & Finlay, 1996	MB (18) > 3 yrs of age	CEP 500 mg/m ² /day,* thiotepa 300 mg/m ² /day, etoposide 250 mg/m ² /day, Au SCR	if gross RD: EFS in 1 of 7 if minimal RD: EFS in 5 of 11	33-mo EFS 33%	median 6 mos
	MB (13) < 3 yrs of age	VCR/bisplatin/CPM/etoposide, CEP 500 mg/m ² /day,* thiotepa 300 mg/m ² /day, etoposide 250 mg/m ² /day, Au SCR		25-mo EFS 37.8%, over-all survival 66.1%	
Dupuis-Girard, et al., 1996	MB (20)	busulfan, thiotepa, Au BMT		31-mo EFS 50%	
Graham, et al., 1997	MB (19), PNET (3)	CPM 1.5g/m ² melphalan 25–60 mg/m ² po busulfan 37.5 mg/m ² melphalan 180 mg/m ² po, CEP 700 mg/m ² /day, etoposide 500 mg/m ² /day, Au SCR	MB: PD 15 of 19, NED 4 of 19 at 27–49 mos, PNET: SD 2 of 3 at ≥ 34 & ≥ 33 mos	MB: median EFS 10.5 mos	
Dunkel, et al., 1998	MB (23)	CEP 500 mg/m ² , thiotepa 300 mg/m ² , etoposide 250 mg/m ² , Au SCR		median 6 mos, 3-yr EFS 34 ± 10%, 3-yr sur 46 ± 11%	median 7 mos
Lefkowitz, et al., 1990	MB (7)	CCNU 100 mg/m ² cisplatin 90 mg/m ² VCR 1.5 mg/m ²	6 of 6 (100%), CR 4 of 6 (median 24 mos), PR 2 of 6 1 of 15 (7%)		18.5 mos
Friedman, et al., 1992	MB (15)	CEP	1 of 14 (7%)		
Gentet, et al., 1995	MB (14)	ipropilatin	18 of 25 (72%)		
	MB (26)	CEP			
Ashley, et al., 1996	MB (7)	etoposide 50 mg/m ² /day	following 2 cycles: PR 6 of 7 (86%); SD 1 of 7 (14%)		range 2–4 mos
Chamberlain & Komanik, 1997	MB (8)	etoposide 50 mg/m ² /day, dexamethasone (6 patients)	following 1 cycle: PR or SD 5 of 8 (63%); PD 3 of 8 (38%)	median 5.5 mos	
* Au = autologous; CR = complete response; NED = no evidence of disease; PR = partial response; SD = stable disease; TTP = time to disease progression.					

High-dose Chemotherapy With Autologous Stem Cell or Bone Marrow Rescue. High-dose chemotherapy with autologous SCR or autologous BMR has been the subject of intense investigation and scrutiny in an effort to improve the poor outcomes in children. Stem cell rescue involves

harvesting autologous bone marrow or, preferably, peripheral stem cells by using pheresis techniques and subsequently reinfusing them after provision of high-dose myeloblastic chemotherapy.

In an early study by Finlay, et al.,[27] patients with recurrent medulloblastoma/PNET were treated with high-dose thiopeta and etoposide followed by infusion of autologous bone marrow. In six of 12 patients who could be evaluated for response, two demonstrated objective response. Median survival was 3.2 months with no event-free survivors. In all four patients who died of disease (as opposed to toxicity-related causes) significant residual tumor was demonstrated at the time at which BMT was performed, which has prompted the more recent approach of either surgically removing the recurrent tumor or using chemotherapy to cause cytoreduction to a state of minimal residual disease prior to initiation of high-dose chemotherapy.[27]

In a subsequent study, Dunkel and colleagues[22] reported on 23 patients with recurrent medulloblastoma who were treated with carboplatin, thiopeta, and etoposide followed by autologous SCR. In 18 of these patients, disseminated disease at relapse (M_{1-4}) was revealed. All of the patients had previously undergone radiotherapy, chemotherapy, or both in combination. Surgical resection or conventional chemotherapy was used prior to treatment to reduce tumor bulk. The 3-year EFS rate was $34 \pm 10\%$ and the 3-year survival rate was $46 \pm 11\%$. The children with gross residual disease prior to high-dose chemotherapy again fared poorly when compared with those who entered the study with minimal residual disease. More recently, Dunkel and Finlay[21] published a review of the data in patients with recurrent medulloblastoma who were treated with a combination of carboplatin, thiopeta, and etoposide followed by autologous SCR (CCG 9883 or Memorial Sloan-Kettering Cancer Center 89-173 protocol). The addition of carboplatin was motivated by the dismal results seen with the combination of thiopeta and etoposide alone. Tumors recurred in 13 of 21 patients with a median time to disease progression of 7 months. Median survival following recurrence was 6 months, with a 3-year EFS rate of 34%. [21]

In another study,[37] patients with recurrent brain tumors were treated with three different high-dose chemotherapy regimens. Of 18 patients with recurrent medulloblastoma, the median EFS was 10.5 months. The site of tumor recurrence was a significant factor in terms of disease progression following autologous BMR. Of six children with localized recurrences, four remain disease free at 27 to 49 months following transplant. Conversely, in the 12 patients with more widespread disease at presentation, progression was shown in all cases following the procedure. With regard to this treatment modality for PNETs, two of three patients in that study were disease free at 33 and 34 months, respectively, posttreatment ($p = 0.0017$). [36]

Although most of this data suggests that high-dose chemotherapy combined with autologous SCR results in longer EFS, because randomized trials have not been performed, the interpretation of the results remains limited. In addition, toxicity-related consequences are substantial, including death, serious infection, and venoocclusive disease. Despite these factors, autologous SCR clearly benefits a subset of patients, especially those with locally recurrent disease (not involving the brainstem) and without evidence of dissemination. Unfortunately, because bulky disease and distant spread of tumor are present in many children at the time of recurrence, this treatment is irrelevant in these patients.[26]

Oral Agents. Numerous individual agents, including cisplatin, carboplatin, cyclophosphamide, vincristine, and parenterally administered etoposide, have been attempted in the setting of recurrent medulloblastoma/PNET, and the success rates and/or toxicity have varied. Low-dose daily oral etoposide has been used to treat seven children with recurrent medulloblastoma, all of whom had been previously treated with cytotoxic agents, including parenteral etoposide.[4] Six of seven children had previously undergone radiotherapy. Following two cycles of oral etoposide, partial tumor response was seen in six (86%) of seven children and stable disease was demonstrated in the remaining patient. The authors of this study postulated that the constant dosing caused sustained inhibition of topoisomerase II function (which normally functions to repair DNA), therefore causing accumulation of lethal DNA damage to tumor cells. Also, the ability of the drug to penetrate the blood-brain barrier in the setting of leptomeningeal disease is enhanced and therapeutic levels of drug are attainable.[4] In a subsequent prospective phase II trial conducted by Chamberlain and Kormanik[10] the efficacy of this approach was validated. Eight patients with locally recurrent medulloblastoma were treated with a similar regimen of low-dose oral etoposide. Again, all of the children had previously undergone multiagent chemotherapy (although only one received prior etoposide) and radiotherapy. Following one cycle of chemotherapy, in five (63%) of eight patients a partial response or stable disease was demonstrated. Median duration of response was 6 months in these five patients.[10]

CONCLUSIONS

Several treatment strategies are utilized in the management of medulloblastoma/PNET. Overall, there is general agreement that a gross- or near-total resection is the foundation for successful treatment of these malignant tumors.[12] Although postoperative radiotherapy has provided significant improvement in survival rates in children with malignant brain tumors, the adverse effects are cause for concern. The optimal craniospinal radiation dose has not yet been determined because of the disparity between results of reduced- with standard-dose regimens either alone or in combination with conventional chemotherapy. A balance between the concern for the effects of toxicity of standard radiotherapy on the developing brain, given its known efficacy in improving survival in a disease, and an otherwise grim prognosis still needs to be achieved by further investigations. Hyperfractionated radiotherapy may offer improvements in local disease control in patients with high-risk disease and diminish the radiation-induced short- and long-term effects. Further trials of hyperfractionated radiotherapy are indicated so that the utility either in isolation or combined with chemotherapy can be assessed and its effects can be compared with single-fractionated radiation. Patients in whom a more favorable prognosis is indicated benefit from the provision of fractionation schemes that focus on minimizing late effects as opposed to those with disseminated disease that may require more aggressive treatments. The administration of chemotherapy has been investigated at several time points relative to radiation therapy. It appears that chemotherapy preceding radiotherapy provides no benefit to children in whom there is no evidence of metastatic disease at initial presentation. Conversely, a benefit obtained from intensive preradiation chemotherapy is seen in patients with more advanced disease. Postoperative chemotherapy in the child less than 3 to 4 years of age has been shown in large cooperative studies to be partially effective in controlling the disease until the child is old enough to receive radiation therapy. In addition, the combination of chemotherapy with reduced-dose radiotherapy seems to be an effective combination, both in terms of survival and resultant neurocognitive outcome. The results of treating recurrent disease continue to be disappointing. The use of high-dose chemotherapy with autologous SCR has improved disease control in this setting. New approaches, including intraventricular administration of cytotoxic agents, newer drug combinations, and immunotherapy, are

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Address reprint requests to: Bruce Cohen, M.D., The Cleveland Clinic Foundation, Department of Neurology, Desk S-71, 9500 Euclid Avenue, Cleveland, Ohio 44195.