Chemotherapy for Childhood Medulloblastoma and Primitive Neuroectodermal Tumors

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ABSTRACT

Medulloblastoma is the most common form of childhood brain tumor, and management has evolved over the past two decades. Chemotherapy is now an integral part of the treatment of the majority, if not all, patients with this disease. Medulloblastoma is a chemosensitive tumor, and recurrent disease will often respond to a variety of different chemotherapeutic agents. The use of higher-dose chemotherapy supplemented with aggressive hematological support may improve outcome for patients with recurrent disease. The results of prospective randomized trials and large, single, institutional trials in children with newly diagnosed disease suggest that chemotherapy, when given during and after radiotherapy, improves outcome. This is especially true for children with more extensive disease at the time of diagnosis. Event-free survival rates as high as 85% have been reported in children with newly diagnosed medulloblastomas treated with radiation and adjuvant chemotherapy consisting of CCNU, vincristine, and cisplatinum. At the present time, there is no clear evidence that preradiation chemotherapy improves survival for children with medulloblastoma. In fact, two prospective trials suggest that treatment with pre-irradiation chemotherapy may result in poorer overall outcome than treatment with similar doses of radiation therapy or radiation therapy supplemented by postradiation chemotherapy. There is preliminary evidence that chemotherapy may allow for a reduction in the dose of craniospinal irradiation therapy required to control disease, especially for children with nondisseminated disease at the time of diagnosis. Treatment for infants with medulloblastoma and other primitive neuroectodermal tumors remains suboptimal. Some infants and young children will experience long-term disease control after treatment with chemotherapy alone or chemotherapy followed by radiation when the child is older. High-dose chemotherapy supplemented by autologous bone marrow rescue or peripheral stem cell rescue has been utilized in young infants with promising results. The need for postchemotherapy radiation therapy and the volume of radiotherapy required to control disease remain under study. ***The Oncologist*** *1996;1:381-394*

INTRODUCTION

Primary central nervous system tumors of childhood are the most common form of childhood solid tumors and the leading cause of mortality secondary to childhood malignancies. These tumors are increasing in incidence, may arise in any site in the brain, and are comprised of multiple different histologies. Medulloblastoma is the single most common form of malignant childhood brain tumor, and other tumors which are histologically similar may arise in the cerebral cortex (cerebral primitive neuroectodermal tumors [PNETs]) or the pineal region (pineoblastomas) [1]. Management of medulloblastoma and other childhood PNETs has slowly evolved over the past quarter-century [2-4]. Chemotherapy is now an integral part of the management of the majority, if not all, of childhood medulloblastomas and PNETs [2-5]. This review will summarize the expanding role of chemotherapy in the management of medulloblastoma and other primary central nervous system PNETs, including: A) the use of chemotherapy for patients with recurrent disease; B) its utility as adjuvant treatment of patients with newly diagnosed disease; C) chemotherapy's potential to reduce the volume and amount of radiotherapy needed at the time of diagnosis, and D) data to support chemotherapy's use as initial therapy for younger children.

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General Aspects of Medulloblastoma and Other PNETs

Medulloblastoma and other PNETs are composed predominantly of small cells with little cytoplasm and hyperchromatic nuclei [1]. These tumors frequently display histological heterogeneity with some regions within the tumor demonstrating glial or other types of cellular differentiation. There has been considerable debate in the literature concerning the most appropriate classification of childhood PNETs, and some have postulated that all PNETs, including medulloblastomas, arise from similar cells and should be classified as PNETs and then subclassified based on evidence of cellular differentiation and possibly tumor location. Others have suggested that the term medulloblastoma be maintained for those tumors arising in the posterior fossa and, similarly, "pineoblastoma" for tumors arising in the pineal region [2, 6]. The most recent World Health Organization classification of childhood brain tumors has maintained the latter approach, as medulloblastoma is considered a distinct subvariety of embryonal tumor and separate classifications are maintained for other (primarily cortical) PNETs, ependymoblastomas, and pineoblastomas [6].

The management of medulloblastoma continues to evolve.

Specific immunohistological or molecular genetic markers for medulloblastoma or other PNETs have not yet been identified. Immunohistochemical analysis has demonstrated that single, primitive, neuroectodermal cells may have both neuronal and glial intermediate filaments [7]. The majority of PNETs will be synaptophysin-positive. Approximately one-third of patients with medulloblastoma and other PNETs will have an isochromosome 17q abnormality [8].

The management of medulloblastoma continues to evolve [2]. In the 1960s, it was recognized that the employment of presymptomatic craniospinal irradiation for all patients with medulloblastoma increased the overall survival rate [9-11]. Patients treated with conventional doses of craniospinal irradiation (3,600 cGy) and local-boost radiotherapy (total dose, 5,400-6,000 cGy) experienced a five-year, disease-free survival of between 40% and 60%. It was later recognized that a significant number of children with medulloblastoma had disseminated disease at the time of diagnosis, as postoperative analysis of lumbar cerebrospinal fluid and either magnetic resonance imaging (MRI) or myelography of the spine disclosed subarachnoid disease in approximately 30% of patients [10, 12]. Infants and younger children are at even higher incidence for the development of leptomeningeal disease [12].

Prospective randomized studies performed in the late 1970s and early 1980s demonstrated that children with medulloblastoma could be broadly separated into two risk groups [10, 13]. Those children with disseminated disease at the time of diagnosis and possibly those whose tumors were larger, had brain stem involvement and/or were not amenable to total resections, and carried a poorer prognosis with an overall survival rate five years after radiation therapy alone of 40%. Patients with one or more such characteristics were designated as "poor-risk" patients. In contrast, those patients with localized disease at the time of diagnosis who had tumors amenable to aggressive resections had an approximate 50%-60% rate of survival at five years and were designated as "average-risk patients." Subsequent studies have redefined these risk parameters. It is clear that the extent of dissemination at the time of diagnosis is the single most powerful predictive factor, as children with disseminated disease have a poorer survival rate than those without frank evidence of dissemination. When analysis has been controlled for other factors, the presence of brain stem involvement and the size of the tumor at the time of diagnosis have not been found to be independently predictive of outcome [2, 4, 14]. For those children with localized disease at the time of diagnosis, extent of resection seems to impact on outcome, as patients with more extensive resections (total or near-total resections) have a more favorable outcome than those whose tumors are less aggressively resected [14]. Age remains an independent predictor of outcome for unclear reasons; younger children carry a poorer prognosis than older children [2, 4, 10, 14].

A variety of immunohistochemical and biological tumor characteristics have been evaluated for potential clinical significance, including DNA ploidy, mitotic index, differentiation lineage, expression of the *MDR* gene, and TRK expression [15-20]. The conclusions from many of these studies are either contradictory or based on an insufficiently large number of patients to establish the independent prognostic significance of any single factor. Work is presently under way trying to better define prognostic factors for children with medulloblastoma and other PNETs. The potential significance of identifying prognostic factors is elucidated by the recent separation of childhood atypical teratoid tumors from the subgrouping of children with PNETs [21]. Childhood atypical teratoid tumors have a specific immunohistochemical profile and, in up to one-third of the cases, a different genetic abnormality than childhood medulloblastoma (the presence of monosomy [22]). Childhood atypical teratoid tumors carry a dismal prognosis, as the vast majority of patients are dead within 18 months of diagnosis.

The significance of the separation of children with medulloblastoma into various risk groups has taken on even more significance when the prospective studies undertaken in the 1970s and early 1980s demonstrated that children with "poor-risk disease" benefited from the addition of chemotherapy, while improved survival could not be demonstrated in children with "average-risk disease" [10]. These results led to a generation of studies for children with poor-risk disease utilizing more aggressive chemotherapy in an attempt to improve survival, while those patients with average-risk disease were treated on protocols primarily directed at reducing the amount of radiotherapy given in attempts to decrease the late effects of treatment [2, 22]. The concept that children without poor-risk factors do not benefit from the addition of chemotherapy has been questioned. At best, children with average-risk disease treated with radiotherapy alone have a 60%-70% five-year survival [10, 11, 13, 22-25]. In contrast, some series of children with poor- or intermediate-risk disease are reported to have survival rates as high as 85% at five years.

An important related issue in the management of children with medulloblastoma or other PNETs is the quality of life of long-term survivors [26]. It is now well recognized that many long-term survivors have significant neurocognitive, endocrinologic, and psychologic sequelae [2, 26]. Although a variety of factors accounts for these sequelae, radiation therapy has been implicated as a primary cause of damage, especially in very young children. For this reason, there has been significant interest in utilizing chemotherapy as the primary therapy for infants and young children with medulloblastoma and other PNETs. This approach is used with the hope that it may obviate the need for radiation therapy and, at the very least, delay the need for radiation therapy, possibly limiting the volume of radiation required.

A final general issue is the management of children with PNETs outside the posterior fossa [27, 28]. Data suggest that children with nonposterior fossa PNETs carry a poorer prognosis, possibly because of younger age at time of diagnosis or because such tumors (especially pineoblastomas) are frequently disseminated early in the course of illness. Nonposterior fossa tumors may also be biologically different from medulloblastomas. Most management schema have included these patients within treatment regimens designed for children with poor-risk medulloblastoma. Although the concept that cortical and pineal tumors carry a poorer risk than posterior fossa tumors is likely true, such a conclusion is based on relatively scant data.

Treatment of Medulloblastoma at Recurrence

As can be inferred from the previous discussion, about 20%-50% of patients with medulloblastoma/PNET will experience a recurrence of their tumor despite initial surgical resections, radiation therapy, and chemotherapy. With any conventional treatment strategy, the prognosis for patients with recurrent disease is grim, with few long-term survivors. Reports from the Children's Hospital of Philadelphia, Stanford University Medical Center, the Royal Marsden Hospital, London, the Texas Children's Hospital and MD Anderson Cancer Center noted either no or very few long-term survivors following recurrence [29-32]. Furthermore, the median survival time following recurrence was short, in most reports less than 12 months. Interestingly, the duration of survival did not appear to correlate with duration of initial remission.

Surgery may play a role in the management of recurrent medulloblastoma; however, this is restricted to resection of localized recurrence, either in the original primary tumor site (representing less than one-third to one-half of all recurrences) or, less commonly, in a single site of metastatic recurrence either supratentorially or in the spinal cord. Re-irradiation may be employed in patients whose recurrences develop several years out from initial radiotherapy, particularly for patients with localized recurrences. Current advanced technologies permitting highly focused irradiation (either conformal-focused CT-treatment planned, fractionated stereotactic irradiation; or even single-fraction stereotactic radiosurgery) may be of benefit in limiting morbidity of re-irradiation. Nevertheless, surgery and irradiation, either alone or in conjunction with additional conventional chemotherapy, will only rarely produce long-term survival rates following recurrence of medulloblastoma. Several reports over the last decade have documented objective radiographic responses of recurrent medulloblastoma to several chemotherapeutic agents, including cisplatin, carboplatin, cyclophosphamide, and etoposide, both intravenously and orally [33-40]. Despite response rates as high as 80% in some studies, durable survivals have rarely been documented in any of these phase II trials.

Beginning in the mid-1980s, high-dose chemotherapy with autologous bone marrow rescue began to be explored for the treatment of patients with recurrent medulloblastoma [41]. Since only a small minority of patients with medulloblastoma have bone marrow and/or bone metastases, autologous hematopoietic stem cells free of detectable contaminating tumor cells are potentially available for the majority of patients.

In a first pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue conducted between 1986 and 1992, 45 patients with recurrent brain tumors were treated; nine of these had medulloblastoma and three had supratentorial PNETs [41]. Only six of these 12 were evaluable for response and two of six showed radiographic partial responses. No patient survived beyond 26 months from

treatment. Five of these 12 patients (42%) died from treatment-related morbidity, compared with a toxic mortality rate for the whole study patient population of 16%. These disappointing early findings, both in terms of lack of efficacy and unacceptable toxic mortality, reflected, at least in part, the more heavily pretreated status of the majority of the medulloblastoma/PNET patients.

In a more recent trial of high-dose thiotepa and etoposide with the addition of high-dose carboplatin followed by autologous (either bone marrow or peripheral blood) hematopoietic stem cell rescue conducted between 1990 and 1995, 23 patients with recurrent medulloblastoma were treated (Table 1) [42]. Three patients (13%) died of treatment-related toxicity. Eight patients (35%) survived without progression at a median of 36 months from treatment (range from 10 to 63 months). The Kaplan-Meier estimates of progression-free survival and overall survival at three years were, respectively, 30% and 41%. Factors suggestive (but not statistically predictive, possibly in view of small patient numbers) of improved survival were the absence of leptomeningeal dissemination at the time of recurrence and the achievement of minimal residual disease status prior to the use of high-dose chemotherapy. These data indicate, for the first time, a therapeutic strategy that may produce durable survival for a proportion of patients with recurrent medulloblastoma.

Additional reports of the use of high-dose chemotherapy with autologous bone marrow rescue for patients with medulloblastoma have emanated from France (busulfan and thiotepa) and the Pediatric Oncology Group (POG) (melphalan and cyclophosphamide) (Table 1) [43-45]. In the French study, six patients with medulloblastoma were treated, three achieving partial responses and two surviving without progression at the time of their publication. In the POG study, eight children with recurrent medulloblastoma were treated; there were three partial and one complete radiographic responses, with two patients surviving 24 months. However, three patients (38%) died of treatment-related complications.

Young children with medulloblastoma who experience a relapse following initial treatment with chemotherapy alone without initial irradiation may have improved survivals if treated with high-dose chemotherapy and stem cell rescue followed by irradiation. The French have recently reported their experience, in which they used only local-field irradiation following such treatment for patients without evidence of failure beyond the primary site at recurrence [45]. At the time of publication, none of 11 children so treated had relapsed further. However, the survival for patients with disseminated disease at relapse was poor, with all patients dying of progressive disease.

The reported trials of high-dose myeloablative chemotherapy with stem cell rescue offer grounds for some cautious optimism in the treatment of patients with recurrent medulloblastoma. What remains unclear from these pilot studies is which proportion of the total population of patients with recurrent medulloblastoma can achieve a state of minimal residual tumor and thereby benefit maximally from such therapy. A multicenter cooperative group trial, randomized or otherwise, enrolling all patients with first relapse medulloblastoma onto a study would be the only way to clarify this issue.

Adjuvant Chemotherapy

The efficacy of chemotherapy, when added to radiotherapy, for newly diagnosed children with medulloblastoma was initially demonstrated by two large, prospective, independent studies performed by the Children's Cancer Group (CCG) and the International Society of Pediatric Oncology (SIOP) in the late 1970s and early 1980s (Table 1) [10, 13]. In both studies, patients were randomized to receive either radiation therapy alone (3,600 cGy craniospinal plus a local tumor boost to a local tumor dose of 5,400-5,600 cGy) or identical radiation therapy plus vincristine therapy during irradiation and postradiotherapy cycles of CCNU and vincristine. For children in the CCG trial, the postradiotherapy chemotherapy regimen also included prednisone for the first 14 days of each post-irradiation cycle. These studies can be criticized due to the unavailability of CT scanning in some institutions and thus an inability to truly assess the amount of postoperative residual tumor, as well as the incomplete postoperative staging of some patients for disseminated disease. However, for the first time, a statistical benefit for the addition of chemotherapy for some subjects of children with posterior fossa medulloblastoma was demonstrated. In the SIOP trial, children with brain stem involvement at diagnosis, treated with irradiation and chemotherapy, had a significantly higher five-year, event-free survival than the children who received treatment with radiation alone. In the CCG trial, the estimated five-year, event-free survival was 60% for children treated with irradiation and chemotherapy and 50% for those patients who were treated with radiation therapy alone, a difference which was not statistically significant. Patients with higher T stages (i.e., those patients with larger bulk disease at the time of diagnosis) alone did not statistically benefit from the addition of chemotherapy. However, for the 30 patients in the study with the most extensive tumors, both large primary-site disease and metastatic disease, event-free survival was markedly better in the group receiving chemotherapy (48% versus 0%, $p = 0.006$). Overall survival was also significantly prolonged by chemotherapy for patients with more extensive lesions.

Table 1. Therapeutic strategies and survival rates for patients with medulloblastoma and other primary central nervous system PNETs

Disease	Treatment modality	Number of patients	Results	Investigator
Posterior fossa medulloblastoma	Craniospinal + local-boost radiotherapy + vincristine during radiotherapy + cisplatinum, CCNU, vincristine	63	• Progression-free survival for the entire group at five years was 85% ± 6%. • Three patients succumbed to a second malignancy, and the overall five-year, event-free survival was 83% ± 6%. • Children who had received reduced-dose radiotherapy had similar outcomes to those who had received conventional-dose therapy. • Patients with metastatic disease at the time of diagnosis had a five-year, progression-free survival rate of 57% ± 15% as compared to 90% ± 6% for those with localized disease at the time of diagnosis.	*Packer,* 1994 [4]
Medulloblastoma	Radiation therapy or radiation therapy + vincristine during irradiation + postradiotherapy of CCNU + vincristine	233	• Five-year, event-free survival was 60% for children with brain-stem involvement at diagnosis and 50% for patients treated with radiation therapy alone. • Patients with higher T stages did not statistically benefit from the addition of chemotherapy. • For the 30 patients in the study with the most extensive tumors, event-free survival was markedly better in the group receiving chemotherapy (48% versus 0%; $p = 0.006$). • Overall survival was also significantly prolonged by chemotherapy for patients with more extensive lesions.	*Evans,* 1990 [10]
Medulloblastoma	Radiation therapy or radiation therapy + vincristine during irradiation + postradiation therapy of CCNU + vincristine	286	• Children with brain-stem involvement at diagnosis had a significantly higher five-year, event-free survival than the children who received radiation alone.	*Tait,* 1990 [13]
Medulloblastoma	Preradiation chemotherapy consisting of vincristine, procarbazine, methotrexate or radiation therapy alone	364	• Five-year event-free survival was 58% ± 2.7% for all patients. • Five-year event-free survival of 56.3% ± 6.5% for patients receiving preradiation chemotherapy versus 52.8% ± 6.1% for postradiation chemotherapy only. • Five-year event-free survival of 75% ± 7.2% to 41.7% ± 8.2% for low-risk disease. • Average-risk patients treated with preradiation chemotherapy and reduced-dose radiation therapy had poorer rate of survival (41.7% ± 8% than any other subgroup.	*Bailey,* 1995 [23]
Recurrent medulloblastoma	High-dose thiotepa + etoposide + high-dose carboplatin followed by autologous hematopoietic stem cell rescue	23	• 3 died of treatment-related toxicity. • 8 survived without progression at a median of 36 months from treatment. • At 3 years, Kaplan-Meier estimates were 30% progression-free survival and 41% overall survival.	*Finlay,* 1994 [42]
Medulloblastoma	Chemotherapy (high-dose busulfan + thiotepa) with autologous bone marrow transplantation	35	• 77% relapsed at median 6.3 months from diagnosis.	*Kalifa,* 1992 and *Dupuis-Girod,* 1996 [43, 45]
Recurrent medulloblastoma	High-dose melphalan + cyclophosphamide + autologous bone marrow rescue	6	• 3 had partial responses. • 2 had survival without progression.	*Mahoney,* 1996 [44]

Disease	Treatment modality	Number of patients	Results	Investigator
Medulloblastoma	Busulfan + thiotepa + autologous bone marrow transplantation	8	• 3 had partial and 1 had complete radiographic response. • 2 survived 24 months. • 3 died of treatment-related complications.	*Dupuis-Girod,* 1996 [45]
PNETs of the posterior fossa and other central nervous system sites	Craniospinal + local-boost radiotherapy + concomitant vincristine during radiotherapy + prednisone or "eight-drugs-in-one-day" therapy prior to radiotherapy + craniospinal + local-boost radiotherapy + eight post-radiotherapy cycles of "eight-drugs-in-one-day" therapy	304	• Event-free survival at a median of four years of follow-up was 55%. • Initially, for children with less-extensive disease at the time of diagnosis and now for the group as a whole, there is a statistical difference in survival in those patients who received the control arm of CCNU and vincristine (event-free, five-year survival 60%) as compared to those who received pre- and postradiation "eight-drugs-in-one-day" chemotherapy (five-year, event-free survival 51%).	*Zelzer,* 1995 [47]
Medulloblastoma	Postoperative radiation therapy alone or craniospinal radiation + chemotherapy (MOPP regimen of nitrogen mustard, vincristine, prednisone and procarbazine)	71	• Five-year event-free survival of 68% for patients receiving radiation + chemotherapy. • Five-year event-free survival of 57% for patients receiving radiation alone.	*Krischer,* 1991 [48]
High-risk medulloblastoma (residual tumor in primary site and/or tumor dissemination)	Neoadjuvant cisplatin and etoposide	8	• One complete and six partial responses prior to irradiation, with the final patients showing stable disease. • The initial evaluation of the "eight-drugs-in-one-day" chemotherapy regimen demonstrated 12 radiographic responses of 21 evaluable cases of newly diagnosed medulloblastoma in a four-to-six-week window prior to irradiation.	*Kovnar,* 1990 [49]
Medulloblastoma	Procarbazine + radiation + concomitant hydroxyurea	47	• Five-year progression-free survival and overall survival rates were 63% and 68% (low-risk disease). • No difference in patients who received reduced-dose radiotherapy compared to patients who received full-dose craniospinal radiation therapy. • Of the 17 patients with nondisseminated disease at diagnosis in this series who relapsed, only one initially recurred outside the primary tumor site.	*Levin,* 1988 [55]
Non-disseminated medulloblastoma	Reduced-dose craniospinal radiation + full-dose local-boost radiotherapy + adjuvant CCNU, vincristine, and cisplatinum chemotherapy	68	• Overall progression-free survival at three years is 80% ± 6%.	*Packer,* 1995 [56]
Infantile brain tumors	Surgery + MOPP chemotherapy	13	• Five-year progression-free survival of approximately 55%.	*Baram,* 1987 [58]
Malignant brain tumors	Postoperative chemotherapy (vincristine + cyclophosphamide followed by cisplatin + etoposide) + delayed radiation	102	• Median time to relapse was nine months. • 34% remained progression-free at median of two years from diagnosis. • No patients relapsed beyond 26 months of diagnosis.	*Duffner,* 1993 [59]
Medulloblastoma	12 months of "eight-drugs-in-one-day" chemotherapy	46	• Median time to progression was six months. • Three-year progression-free survival was 22%. • One relapse beyond 21 months from diagnosis.	*Geyer,* 1994 [60]
Medulloblastoma	Intensive induction chemotherapy (cisplatin + high-dose cyclophosphamide + etoposide + vincristine with G-CSF) followed by a single consolidation cycle of myeloablative chemotherapy (thiotepa + etoposide + carboplatin) with stem cell rescue	19	• 80% completed induction chemotherapy and proceeded to consolidation. • In 13 eligible children, two-year, event-free and overall survivals from diagnosis are 51% and 61%.	*Finlay,* 1996 [62]

During the same era that the SIOP and CCG trials were undertaken, *McIntosch* and colleagues reported that 81% of 21 children treated with cyclophosphamide and vincristine after radiotherapy were alive and free of disease at a median of six years after diagnosis [46]. It is difficult to interpret this study since selection criteria utilized to enter patients in this study were not clearly delineated.

Based predominantly on the finding that children with more extensive disease at the time of diagnosis (either at the primary tumor site or disseminated throughout the neuroaxis), a variety of studies were begun on a national or institutional basis attempting to improve survival by intensifying the post-irradiation chemotherapy. The largest nonrandomized study was performed by collaborators at the Children's Hospital of Philadelphia, Children's National Medical Center (Washington, DC), and Children's Medical Center of Dallas (Table 1). In total, 63 children with posterior fossa medulloblastomas were treated. To be eligible for study, children had to be older than three years of age and had to have fulfilled poor-risk criteria including subtotal resection, evidence of metastatic disease at the time of diagnosis, and/or brain stem involvement (Table 1) [4]. Children in the study were treated with craniospinal (3,600 cGy for older patients, 2,400 cGy for younger patients) and local-boost (total dose 5,400 cGy) radiotherapy and vincristine during radiotherapy followed by eight six-week cycles of cisplatinum, CCNU, and vincristine. Forty-two patients had brain stem involvement, 15 had metastatic disease at the time of diagnosis, and 19 had undergone a subtotal resection. These patients were treated sequentially between 1983 and 1991 and at follow-up in early 1994, progression-free survival for the entire group at five years was 85% ± 6%. Three patients in this series succumbed to a second malignancy and the overall five-year, event-free survival was 83% ± 6%. In this study, children who had received reduced-dose radiotherapy had similar outcomes to those patients who had received conventional-dose radiation therapy. Patients with metastatic disease at the time of diagnosis had a five-year, progression-free survival rate of 67% ± 15%, as compared to 90% ± 6% for those patients with localized disease at the time of diagnosis.

While the single-arm study utilizing CCNU, vincristine, and cisplatinum was being performed, a study was being completed by the CCG prospectively treating children with similarly labeled poor-risk disease. Treatment for these children included either craniospinal and local-boost radiotherapy and concomitant vincristine chemotherapy during radiation therapy and eight six-week cycles of post-irradiation, CCNU, vincristine, and prednisone; or the eight-drugs-in-one-day therapy for two cycles prior to radiation therapy, followed by craniospinal and local-boost radiotherapy, and then eight postradiotherapy cycles of the eight-in-one-day therapy. This study has only been reported in abstract form, and a total of 304 patients with PNETs (of the posterior fossa and other sites in the nervous system) were randomized (Table 1) [47]. The event-free survival at a median of four years of follow-up is 55%. However, initially for those children with less extensive disease at the time of diagnosis (i.e., nonmetastatic disease) and now for the group as a whole, there is a statistical difference in survival in those patients who received the control arm of CCNU and vincristine (event-free, five-year survival 60%) as compared to those who received pre- and postradiation eight-drugs-in-one-day chemotherapy (five-year, event-free survival, 51%).

In a multicenter, randomized, clinical trial performed during the late 1980s and early 1990s by the SIOP, 364 children with biopsy-proven medulloblastoma were randomly assigned to either receive pre-irradiation chemotherapy or treatment with radiation therapy alone (Table 1) [23]. In this study, children were separated into high- and low-risk categories based on the amount of gross residual disease following surgery, evidence of brain stem involvement at the time of diagnosis, and/or evidence of metastases at the time of diagnosis. All children were given 5,500 cGy to the primary tumor site. Children with so-called low-risk disease were further randomized to receive either 3,600 cGy or a reduced-dose (2,500 cGy) of craniospinal irradiation. The chemotherapy regimen consisted of vincristine, procarbazine, and methotrexate given over a six-week period before radiation therapy. Those children with high-risk disease received vincristine and CCNU after radiotherapy. In this study, the estimated five-year, event-free survival for all patients was 58% ± 2.7%. There was no evidence of benefit from the pre-irradiation chemotherapy for patients with higher-risk disease, as those who received preradiation chemotherapy had a 56.3% ± 6.5% five-year event-free survival as compared to 52.8% ± 6.1% for those receiving only postradiation chemotherapy. There was also no evidence that the addition of preradiation chemotherapy improved survival in any risk group. For children with low-risk disease, the five-year, event-free survival rate ranged between 75% ± 7.2% and 41.7% ± 8.2%. The only statistically significant finding in this study for children with average-risk disease was that children who were treated with pre-irradiation chemotherapy and reduced-dose radiation therapy had a poorer rate of survival (41.7% ± 8%) than any other subgroup of patients. This study is difficult to interpret given that the entire group of patients was split into six different subgroups; however, it is of concern that the patients who had the poorest event-free survival were those who were treated with delayed radiation therapy and no adjuvant chemotherapy after the completion of irradiation.

Another phase III study of patients with newly diagnosed medulloblastoma was conducted by the POG between 1979 and 1986 (Table 1) [48]. In this randomized trial, 71 patients were treated with either postoperative radiation therapy alone or craniospinal radiation therapy and chemotherapy. The chemotherapy regimen employed was the MOPP regimen, consisting of nitrogen mustard, vincristine, prednisone, and procarbazine. The five-year, event-free survival for the group receiving radiation and chemotherapy was 68% compared to 57% for those receiving radiation alone. The small numbers of patients randomized in this study made it difficult to evaluate the impact of various risk criteria upon the benefit of chemotherapy, however, there was an overall improvement in survival with adjuvant chemotherapy throughout the various risk categories.

These studies, taken in total, suggest that adjuvant chemotherapy is of benefit for children with medulloblastoma (PNETs of the posterior fossa). Randomized studies have only demonstrated this improvement in children who have received chemotherapy during and after irradiation. The trials which have utilized pre-irradiation chemotherapy have either shown no advantage for the addition of the pre-irradiation chemotherapy or, as in the recent CCG trial and in one arm of the recent SIOP, poorer survival for children treated with pre-irradiation chemotherapy. This seems to be especially true for those children with so-called average-risk disease.

The role of adjuvant chemotherapy for children with non-posterior fossa PNETs has not been well demonstrated [27, 28]. This is partially due to the relatively small numbers of patients available for study. In the CCG trial utilizing pre-irradiation and post-irradiation chemotherapy with the "eight-drugs-in-one-day" regimen compared with so-called standard treatment with radiation therapy plus CCNU and vincristine, children with both pineal-region PNETs and nonposterior fossa non-pineal PNETs were separately analyzed (Table 1). For the supratentorial primitive neuroectodermal group as a whole, 44 patients were randomized to receive one of the two different treatments, and the three-year progression-free survival was 45% ± 8%. Similar to the medulloblastoma study, advanced M stage was a factor which suggested poorer prognosis. Twenty-five children with PNETs of the pineal region (pineoblastomas) were treated. Eight were less than 18 months of age and were nonrandomly treated with the "eight-drugs-in-one-day" chemotherapy regimen. The remaining 17 patients were randomized between the two treatments. All infants in this study developed progressive disease a median of four months from the start of treatment. Of the 17 older patients, the overall three-year progression-free survival was 61% ± 13%. Interestingly, outcome was better for children with pineoblastomas than for those with other types of supratentorial tumors treated on the study. The numbers in this study are too small to evaluate the relative efficacy of either of the two chemotherapy regimens.

Although the data remain somewhat inconclusive, the role for chemotherapy in children with average-risk and high-risk disease is now relatively well accepted, especially given the extremely high rates of survival reported by some groups after treatment with postradiation chemotherapy. Studies are presently under way evaluating which chemotherapeutic regimen is most effective in controlling disease. There is significant reluctance to enter children with average-risk (predominantly nondisseminated tumors) on studies which utilize preradiation chemotherapy and delay the initiation of radiation therapy.

At the present time, multiple studies are under way attempting to evaluate the use of more intensive pre-irradiation chemotherapy followed by radiation therapy for patients with poor-risk PNETs. The eligibility for the studies has evolved over time, and most studies now primarily include only those children with posterior fossa tumors who have disseminated disease at the time of diagnosis or large amounts of local disease after surgery and children with nonposterior fossa PNETs. In addition, trials are soon to begin in children with high-risk PNETs utilizing more aggressive chemotherapy during radiation therapy or more intensive chemotherapy following radiation therapy with hematological support (including peripheral stem cell rescue).

Pre-Irradiation Chemotherapy for Newly Diagnosed Medulloblastoma

The rationale for employing chemotherapy following initial diagnosis and surgical resection of medulloblastoma prior to radiation therapy is similar to that in many other solid tumors of both children and adults. Such neoadjuvant chemotherapy provides a "window" of opportunity in which to objectively assess the response of previously untreated tumor to a single drug or combination of drugs. This potentially improves the understanding of which drugs are the most effective to use for a particular tumor in the adjuvant setting and avoids the problem of evaluating drugs in the setting of recurrent disease, at a time when the development of acquired drug resistance might result in the rejection of a drug as inactive when it might otherwise be confirmed as active in the neoadjuvant setting. Documentation of tumor responsiveness in the pre-irradiation time window might prove, for any particular tumor, to be predictive of improved prognosis, permitting more rational tailoring of further treatment (e.g., more intensive treatment for the slow/poor responders, less intensive for the good responders). Another potential benefit of pre-irradiation chemotherapy is that it might render a surgically incompletely resectable tumor completely resectable at a "second-look" procedure. This is likely to be an uncommon

occurrence in medulloblastoma, where the majority of patients achieve a near-total resection at initial surgical intervention.

Several small single-institution trials of neoadjuvant chemotherapy in medulloblastoma have affirmed responsiveness of previously untreated tumor to chemotherapy. *Kovnar* (St. Jude Children's Research Hospital) treated eight children with high-risk medulloblastoma at diagnosis (defined as either residual tumor in the primary site and/or tumor dissemination) with neoadjuvant cisplatin and etoposide for four courses at three-week intervals (Table 1) [49]. This study demonstrated one complete and six partial responses prior to irradiation, with the final patients showing stable disease. The initial evaluation of the "eight-in-one" chemotherapy regimen demonstrated 12 radiographic responses of 21 evaluable cases of newly diagnosed medulloblastoma in a four-to-six-week window prior to irradiation [50]. Additional phase II response data for neoadjuvant chemotherapy in newly diagnosed medulloblastoma have been published for melphelan, cyclophosphamide, and cisplatin/vincristine [51-53].

One concern regarding neoadjuvant chemotherapy has been that if inadequate chemotherapy is used for a varying period of time prior to initiation of definitive chemotherapy, then the consequence might be poorer disease-free survival than achieved by either irradiation alone or irradiation followed by adjuvant chemotherapy. Such concerns have more than just a theoretical basis. The CCG study of average- and high-risk medulloblastoma (CCG-921) conducted between 1987 and 1991 which compared two chemotherapy regimens has been discussed previously. The "standard" arm of vincristine, CCNU, and prednisone given during and after irradiation was more effective. An alternative explanation for the poorer outcome for children receiving pre-irradiation chemotherapy is that the delay in irradiation by chemotherapy (independent of the kind of chemotherapy used) may result in a poorer outcome in a highly radiation-responsive tumor such as medulloblastoma.

An additional randomized cooperative group study lends credence to the concern that chemotherapy prior to irradiation might result in poorer outcome than with either irradiation alone or irradiation followed by adjuvant chemotherapy. In the second trial of the International Society of Pediatric Oncology (SIOP II), patients with low-stage medulloblastoma, as discussed above, received either standard-dose or reduced-dose neuraxis irradiation, either alone or preceded by neoadjuvant chemotherapy [23]. The results of this study indicated that the patients who received reduced-dose irradiation preceded by chemotherapy with vincristine, procarbazine, and intermediate-dose methotrexate had a poorer outcome than each of the three other groups with low-risk disease.

A POG trial evaluating the impact of neoadjuvant chemotherapy upon overall outcome is currently under way. Patients with high-risk medulloblastoma are randomized to receive either neoadjuvant chemotherapy prior to delayed irradiation or immediate irradiation followed by post-irradiation adjuvant chemotherapy. The results of this trial may better clarify the role of pre-irradiation chemotherapy for children with medulloblastoma.

Chemotherapy Plus Reduced-Dose Radiation Therapy

As stated previously, there are significant concerns regarding the cognitive outcome of children treated with full-dose craniospinal and local-boost radiotherapy, especially in younger children. One approach to reducing the degree of neurocognitive sequelae has been to utilize chemotherapy with reduced-dose craniospinal radiation therapy in the hope that the addition of chemotherapy would compensate for the reduction in radiotherapy. Early reports of randomized trials which attempted to reduce the amount of radiotherapy alone in children with nondisseminated medulloblastomas suggested a higher rate of relapse outside the primary site and poorer overall disease-free survival in patients treated with reduced-dose radiotherapy [22]. However, update of a randomized trial performed by the CCG and the POG raises the question of whether children treated with reduced-dose craniospinal radiotherapy actually do less well, as the difference in event-free survival between those children who received 3,600 cGy of craniospinal radiation therapy and those who received 2,400 cGy of craniospinal radiation therapy is now "significant" at the 0.058 level [54]. Furthermore, with radiation therapy alone, the best survival rates which can be obtained at three to five years range between 50% and 70%. Single-arm studies have demonstrated survival rates higher than 80% for those children receiving radiation and chemotherapy.

In 1988, *Levin* and coworkers reported their experience in 47 patients treated after initial surgery with 14 days of procarbazine followed by radiation and concomitant hydroxyurea (used as a radiosensitizer). The radiation therapy dose to the posterior fossa was 5,500 cGy, 2,500 cGy to the whole brain to children with so-called low-risk disease, 3,500 cGy for patients with high-risk disease, and 2,500 cGy to the spinal axis. The estimated five-year, progression-free survival and overall survival rates were 63% and 68%, respectively, for children with low-risk disease, and there was no difference in those children who received reduced-dose radiotherapy as compared with those who received full-dose craniospinal radiation therapy (Table 1) [55]. Of the 17 patients with nondisseminated disease at diagnosis in this series who relapsed, only one initially recurred outside the primary tumor site.

More recently, the CCG, based on the overall excellent survival reported with the CCNU, vincristine, and cisplatinum post-irradiation chemotherapy approach and the evidence in this preliminary trial that the children who received 2,400 cGy of craniospinal irradiation did not fare as well as those who received 3,600 cGy of irradiation, opened a single-arm study (Table 1) utilizing reduced-dose craniospinal radiation (2,340 cGy) and full-dose local-boost radiotherapy (5,580 cGy) plus adjuvant CCNU, vincristine, and cisplatinum chemotherapy for children with nondisseminated medulloblastoma between the ages of three and 10 years. This trial entered 68 eligible patients, and the overall progression-free survival at three years is 80% ± 6% [56].

Interestingly, prior to the opening of this study, a pilot study was performed at the Children's Hospital of Philadelphia between January of 1988 and March of 1989, treating 10 patients with medulloblastoma utilizing even further-reduced craniospinal radiation therapy (1,800 cGy), a posterior fossa boost to a total dose of 5,400-5,580 cGy, and chemotherapy consisting of vincristine during radiotherapy and six eight-week cycles of vincristine, CCNU, and cisplatinum [57]. The study was halted after the first 10 patients were treated because three patients had relapsed early in the study. However, overall actuarial survival at over six years is 70% ± 20% with no other patients developing progressive disease. Of significant interest in this study is that the mean overall I.Q. of the seven patients surviving at least one year was unchanged from baseline and is 103.

Treatment of Young Children with Newly Diagnosed Medulloblastoma

The youngest children with medulloblastoma suffer double jeopardy. Most studies indicate that the prognosis for children diagnosed in the first three to four years of life is poorer when they are treated with either irradiation alone or in conjunction with chemotherapy [10]. Furthermore, cranial irradiation in young children is attended by unacceptable rates of adverse delayed toxicities, including growth failure and developmental delay [2, 26].

In an attempt to either minimize or avoid the deleterious effects of irradiation, a number of studies have been conducted over the last decade, restricted to children less than 18 to 36 months of age. These children were newly diagnosed with various high-grade brain tumors in which chemotherapy was the mainstay treatment for periods of 12 to 36 months, with either avoidance of irradiation until tumor recurrence or delay of irradiation until three years of age was attained.

The initial enthusiasm for chemotherapy-only strategies for infantile brain tumors was engendered by the reports from the MD Anderson Cancer Center on the use of MOPP chemotherapy without irradiation in 13 children less than 36 months old with medulloblastoma who achieved a five-year, progression-free survival (PFS) of approximately 55% (Table 1) [58]. Following this experience, the POG "Baby" study was initiated in which children less than 36 months of age received chemotherapy (vincristine and cyclophosphamide for two cycles followed by cisplatin and etoposide for one cycle at monthly intervals, repeated until 36 months of age or for at least 12 months of chemotherapy) with delayed irradiation upon completion of the chemotherapy (Table 1) [59]. The median time to relapse of the patients with medulloblastoma in the "Baby POG" study was nine months, and 34% of the medulloblastoma patients remained progression-free at a median of two years from diagnosis. An interesting finding was that no patients relapsed beyond 26 months of diagnosis, raising questions over the necessity of irradiation in those with complete response.

The findings of the "Baby POG" trial have been reiterated in other multicenter trials. The CCG, utilizing 12 months of the "eight-drugs-in-one-day" chemotherapy regimen, administered intensively at two- to four-week intervals without planned irradiation, treated 46 children less than 18 months of age newly diagnosed with medulloblastoma (Table 1) [60]. The median time to progression was six months, with only one relapse beyond 21 months from diagnosis. The three-year, progression-free survival was 22%. The French Society of Pediatric Oncology has recently reported on 35 children with medulloblastoma under three years of age treated with chemotherapy alone, 27 of whom (77%) relapsed at a median of 6.3 months from diagnosis (Table 1) [43, 45]. Similarly disappointing results in young children with medulloblastoma have been reported from Australia [61].

Drawing upon the experience of myeloablative chemotherapy with stem cell rescue in patients with recurrent brain tumors, a pilot study was initiated in 1992 at Memorial Sloan-Kettering Cancer Center and participating institutions (Table 1) [62]. All children with medulloblastoma under three years of age were eligible for study; additionally, children between three and six years of age with disseminated medulloblastoma were also eligible. Children received five cycles of intensive induction chemotherapy (cisplatin, high-dose cyclophosphamide, etoposide, and vincristine, with G-CSF). Bone marrow was harvested either prior to initiation of chemotherapy or following recovery from the first one or two cycles, and a single consolidation cycle of myeloablative chemotherapy (thiotepa, etoposide, and carboplatin) with stem cell rescue followed the completion of induction. If patients had no evidence of residual tumor following completion of induction, then no irradiation was administered following consolidation. Approximately 80%

of children with medulloblastoma successfully completed the induction chemotherapy and proceeded to consolidation. To date, in 13 eligible children, the two-year, event-free and overall survivals from diagnosis are 51% and 61%. Obviously, expanded patient numbers are required to determine if this brief but intensive chemotherapy regimen produces an improved outcome compared to the more conventional chemotherapy strategies reviewed above.

In light of improved strategies for delivery of focused irradiation, one approach that should be evaluated is the addition to these chemotherapy strategies of just localized posterior fossa irradiation, with conformal technique to avoid the internal auditory meati (to minimize hearing loss), the pituitary/hypothalamic region, and the temporal lobes (to minimize short-term memory loss), at least in patients with localized tumor at presentation. While one-half to two-thirds of patients with medulloblastoma will have some component of disease outside the primary site at initial relapse, this approach might nevertheless decrease the incidence of local relapse in patients with just localized disease at initial diagnosis. Evaluations of the patterns of failure in the current cooperative group "baby" trials might provide insight into which infants may or may not be suitable for administration of focused irradiation in conjunction with chemotherapy.

Conclusions

As can be drawn from the previous discussions, treatment for childhood medulloblastoma and other PNETs continues to be actively studied. Both the rate of survival and the quality of life for children with such tumors after treatment with surgery and radiation alone remain suboptimal. Chemotherapy has been utilized for many reasons in children with medulloblastoma, including: salvaging children with recurrent disease, improving survival for children with newly diagnosed disease, and possibly improving the quality of life by reducing or delaying the need for radiotherapy in younger children or for those with nondisseminated disease at the time of diagnosis. Given the apparent biologic heterogeneity of medulloblastoma and the infrequent occurrence of this tumor, definite statements concerning the utility of chemotherapy are difficult to make. However, the best overall survival rates reported for children with this disease have occurred after treatment with aggressive surgery, craniospinal and local-boost radiotherapy, and some form of chemotherapy during and after radiation therapy. The benefits to the patient of preradiation chemotherapy (and thus delay of radiotherapy) have yet to be shown. In fact, the data which exist to date suggest that such approaches may result in poorer overall survival. Despite these uncertainties, it is clear that many children treated with extensive whole-brain irradiation will suffer significant treatment-related sequelae (related, at least in part, to the radiation therapy delivered), and that the overall quality of life of these survivors is inadequate. Until there is a better biologic understanding of medulloblastoma, therapeutic approaches to improve the overall quality of life for children with medulloblastoma and other PNETs will continue to be centered around the use of chemotherapy to at least reduce the dose and volumes of radiotherapy required. Such studies take the risk of resulting in poorer overall rates of survival. High-dose chemotherapy supplemented by autologous bone marrow rescue or peripheral stem cell rescue has been utilized over the past decade for children with medulloblastoma and other PNETs. Preliminary results suggest that such therapeutic approaches result in a high response rate and may also result in durable responses for some children with localized recurrent medulloblastoma. Furthermore, high-dose chemotherapy may be adequate treatment for at least a subset of infants with medulloblastoma; however, with current available means of treatment, the majority of infants and young children, especially those with metastatic disease at the time of diagnosis, will succumb to their illness despite treatment with chemotherapy alone. Better treatment approaches are required for these children and may include the use of higher-dose chemotherapy, often supported by techniques such as autologous bone marrow rescue and supplemented with focused irradiation or possibly with other forms of chemotherapy, such as intrathecal drugs.

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