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Medulloblastoma

Catherine A. Mazzola, MD

Ian F. Pollack, MD*

Address

*Department of Neurosurgery, University of Pittsburgh Children's Hospital,
3705 Fifth Avenue, Suite 3705, Third Floor, Pittsburgh, PA 15213, USA.
E-mail: ian.pollack@chp.edu

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Opinion statement

Medulloblastomas, primitive neuroectodermal tumors of the cerebellum, comprise 20% of all pediatric brain tumors and are the most common solid neoplasm in children. Primitive neuroectodermal tumors are believed to arise from cerebellar granule cell precursors. Occasionally, medulloblastoma occurs in children with genetically linked disorders, such as Turcot's syndrome or Gorlin's syndrome, which is also called basal cell nevus syndrome. Several genes have been implicated in the development of medulloblastoma in children, including Patched-1 and Smoothed. The protein products of these genes function within the sonic hedgehog molecular signaling pathways, which are important in neural development and disease. Through analysis of several well-designed multi-institutional trials, much has been learned about the clinical factors that influence outcome in children with medulloblastomas. Age younger than 3 years, bulky residual disease post-operatively, and metastasis constitute adverse prognostic features and indicate patients who are considered "high risk" for recurrence with standard therapy using 3600 cGy craniospinal radiation in conjunction with a posterior fossa dose of 5400 cGy. Patients lacking these features are considered "standard risk." Chemotherapeutic trials have been developed to assess the safety and efficacy of various multi-agent therapies to improve the poor results of high-risk patients and to allow reduction in the dose of radiation needed to cure standard-risk patients, which may allow a decrease in late cognitive sequelae. Currently, it is policy to evaluate all children with posterior fossa tumors characteristic of medulloblastoma with preoperative, staging neuroimaging studies of the craniospinal axis. Surgical resection is undertaken with the goal of gross total resection. Postoperative neuroimaging studies are compared with preoperative studies to determine the amount of residual disease. Cerebrospinal fluid is obtained from a lumbar puncture done at the conclusion of the surgical resection or 2 weeks after surgery in order to determine microscopic leptomeningeal spread. Children with tumor histopathology consistent with medulloblastoma are enrolled, when possible, in open clinical trials. Chemotherapy and radiation are given as per protocol. The goal of current treatment approaches is to tailor therapy based on clinical risk factors, with intensification of treatment for children with high-risk disease and reduction of radiation therapy for those with standard-risk disease. Evaluation of biologic predictors of outcome, which may further refine treatment stratification, is in progress.

Introduction

Medulloblastoma (MB), which is the most common primary brain tumor in children [1,2•, Class III], arises within the posterior fossa. It resembles histologically other primitive neuroectodermal tumors (PNETs) that occur within the pineal region and supratentorially [3-9], although may result from a different series of

molecular abnormalities [10•, Class II]. It is believed that MB develops from progenitor cells within the external granule layer of the cerebellum or the posterior medullary velum.

Although MBs are often chemosensitive and radiosensitive tumors, they are difficult to treat for several

reasons. First, these tumors have a tendency to disseminate, or spread, throughout the craniospinal axis and occasionally outside the neuraxis, necessitating a systemic approach to therapy and the use of craniospinal irradiation. Secondly, the aggressive treatment needed to cure MB has considerable side effects, especially in the younger pediatric population. Third, these tumors are biologically diverse, and certain subgroups of lesions show rapid tumor progression despite responding to initial therapy. Although tremendous strides have been made in the overall treatment and prognosis of children with MB, the optimal chemotherapeutic and radiotherapeutic regimens for individual patient subgroups have not yet been determined. Accordingly, there are several open clinical trials underway whose goals are the following: 1) to determine whether intensification of chemotherapy or irradiation can improve outcome in patients with high-risk disease; 2) to evaluate the feasibility of reducing the dose of craniospinal irradiation and the volume of the posterior fossa radiation therapy boost by the modest intensification of chemotherapy; and 3) to define molecular and biologic markers that improve outcome predictions in patients with MB.

FREQUENTLY USED INTERNET RESOURCES

The information available to healthcare providers and parents of children with PNET has multiplied exponentially. As the World Wide Web has become more accessible and frequently used by the general public, several Internet web sites with information about MB have been created. Frequently, parents of children with newly diagnosed MB arrive at their doctor's office with references from several websites, appropriate knowledge-based questions, and queries about various treatment protocols. Physicians should be aware of these websites, the information provided by them, and be ready and available to counsel parents of children with MB appropriately (Table 1).

STAGING AND SCREENING

Medulloblastoma may spread contiguously to adjacent central nervous system (CNS) structures, or throughout the craniospinal axis, via cerebrospinal fluid (CSF) seeding. Because of the frequency of metastases at the time of or after diagnosis, children with MB undergo frequent screening, or staging. Two major subgroups of children with MB have been defined; each has distinct prognoses and treatment guidelines (Table 2). Standard risk (also known as "average risk" or "low stage") children with MB have been defined as those older than 3 years of age, with maximal dimensions of residual tumor after surgery measuring less than 1.5 cm², and no dissemination found after staging by magnetic resonance imaging (MRI)/computed tomography (CT) myelography and cytology [11]. High

risk (also known as "poor risk" or "high stage") patients are children under 3 years of age, with more than 1.5 cm² of residual tumor, or those with dissemination found at the time of staging [11]. Historically, patients with standard-risk disease have had 5-year survival rates in the range of 60% to 80%, whereas those for patients with high-risk disease have generally been less than 50% after treatment with craniospinal irradiation. Screening of children with MB may also involve bone marrow aspiration, radiograph of the skeleton, or nuclear medicine (radioactive) bone scans for children with pain in their extremities or abnormal blood cell counts. There are studies underway to investigate the importance of various biologic or molecular markers. At this point in time, however, these studies remain investigational and are not used to stratify therapy.

RADIOLOGIC STUDIES

Neuroimaging is performed in all patients with suspected MB. Computed tomography scans have been the mainstay of diagnosis of brain tumors over the past three decades; however, the sensitivity of MRI is far superior to that of CT for the detection of brain tumors. The entire craniospinal axis is imaged in at least two planes, usually the sagittal and the axial planes, with and without intravenous gadolinium contrast. Magnetic resonance imaging of the brain is repeated postoperatively to provide an assessment of the volume of residual disease. Although surgical resection does not require preoperative MRI, the resection is often aided by knowledge of the tumor's invasion of and proximity to adjacent posterior fossa structures. The tumor may be located entirely within the fourth ventricle of the brain or may directly invade the floor of the fourth ventricle (the brainstem). Magnetic resonance imaging studies may also reveal hydrocephalus. Ventricular drainage, or CSF diversion, at the time of surgery treats progressive ventriculomegaly. Children with signs and symptoms of elevated intracranial pressure, after surgery, may benefit from placement of a ventriculoperitoneal shunt. Once treatment is initiated, routine surveillance neuroimaging with MRI is an important part of the clinical management of children with MB. Screening MRI may detect early, asymptomatic recurrence of disease and may provide additional time for the implementation of salvage therapy, although the significance and optimal timing of surveillance imaging remains controversial [12,13,14••, Class II;15]. Of recent interest, there has been a new and interesting advancement in MRI technology, called *magnetic resonance spectroscopy*. Magnetic resonance spectroscopy allows the detection and relative quantification of various biochemical components of lesions within the CNS. Medulloblastomas have higher than normal choline- and taurine-containing compounds, with moderate

Table 1. Examples of available Internet web sites located for a search of: medulloblastoma

<p>http://www.meds.com/pdq/childmedullo_pro.html</p>	<p>General information about the diagnosis and treatment of pediatric brain tumors, details about the cellular classification of brain tumors and their staging, and categorizes average versus poor risk patients; describes treatment options and overviews; defines current radiation protocols; mentions recurrence rates and provides excellent references to appropriate literature; a web site for general healthcare providers and specialists; not recommended for the general public, because the medical terminology used throughout may be intimidating</p>
<p>http://www.meb.uni-bonn.de/cancernet/2000048.html</p>	<p>A general information web site that is strongly recommended for parents and patients with medulloblastoma; easy to read and understand; contains explanations of staging, treatment, recurrence, and risks; refers questions to the National Cancer Institute Cancer Information Service; Children's Oncology Group is noted as the primary organizer of clinical trials</p>
<p>http://www.cancer.gov</p>	<p>A general information web site that is also strongly recommended for parents and patients with primitive neuroectodermal tumors, with easy to understand definitions and explanations of the diagnosis and treatment (surgery, radiation, and chemotherapy) of medulloblastoma; also contains information about staging, risk, recurrence, and refers parents and patients to National Cancer Institute Cancer Information Service for more information about clinical trials</p>
<p>http://www.stjude.org/diseasestudies/medulloblastoma_PNET.html</p>	<p>A small, informative web site with general information for patients and parents of children with medulloblastoma; offers links to open clinical trials for treatment of primitive neuroectodermal tumors</p>
<p>http://groups.yahoo.com/group/medulloblastoma</p>	<p>A short, introductory invitation to enroll in a medulloblastoma list-server group; this member group reportedly contains 10,000 postings with information about clinical trials, patient histories, and more</p>
<p>http://www.pbtfus.org</p>	<p>A source of support for families with children who have brain tumors; provides news about research programs, funding, and outreach groups; not specific for medulloblastoma; limited clinical information</p>

Table 2. Average risk and high (poor) risk classification of children with medulloblastoma [11]

Average risk	High (poor) risk
<p>Age older than 3 years Postoperative residual disease less than 1.5 cm² No dissemination or spread of disease</p>	<p>Age younger than 3 years Postoperative residual disease greater than 1.5 cm³ Dissemination or spread of disease is present</p>

increases in myoinositol, and significant decreases in N-acetyl-aspartate [16]. The significance of these findings has not yet been determined.

GENETICS OF PRIMITIVE NEUROECTODERMAL TUMORS

Recently, there has been great interest in the definition, classification, and understanding of the cytogenetic abnormalities found in MB. Chromosomal aberrations have been discovered in many MB with loss, gain, or displacement of various segments of chromosomes [2•,17•, Class III]. The most frequent losses detected by comparative genomic hybridization were at chromosomes 17p, 8p, and 11p, and gains were found at chromosomes 7q, 17q, and 18q [17•, Class III]. Some tumors also demonstrated evidence of an isochromosome 17q and N- or L-myc gene amplification [17•, Class III]. Investigation into the molecular mechanisms of the development of MB has shed light onto the shh

signaling pathway [7,8]. Patched-1, a component of the shh receptor, is mutated in 10% to 20% of all sporadic MBs, and has been associated with MB in humans and in animal models [18,19]. A mouse model, heterozygous for Patched-1 mutations has been developed, and it has a high rate of development of MB [20]. There are recent studies that have identified inhibitors of shh signaling, which may provide treatment alternatives to the currently available standard chemotherapy and radiation therapy [21]. Progressive development of microarray technology has allowed scientists to analyze the expression of thousands of genes at once from a single, small tumor specimen. The expression of various cell cycle genes, invasion and migration associated genes, tumor suppressor genes, and regulators of apoptosis and cell death have been irregular in MB compared with normal cerebellar tissue [10•, Class II; 22••, Class III; 23••,24••,25•,26•,27•, Class II].

Treatment

- Better survival rates are the result of clinical trials that attempt to define the best treatment options for children with MB. Clinical trials may compare standard versus new therapies in a randomized, phase III context, or evaluate the safety and activity of novel therapies in a phase I or phase II context. Because the relative frequency of MB in children is low, all children with PNET should be enrolled in clinical trials whenever possible. A multidisciplinary team of specialists facilitates treatment planning.

Surgery

- The goal of surgical resection includes complete, radical resection of tumor, without damage of vital surrounding CNS tissue. Because of the nature of the tumor to grow in the posterior fossa in proximity to the brainstem, there are significant neurologic risks involved with aggressive tumor resection. However, in light of the poor prognosis associated with bulky residual disease, most pediatric neurosurgeons aim for maximal tumor reduction [28]. In some cases, intraoperative neuromonitoring may allow for a safer, yet more aggressive, resection.

Pharmacologic treatment

Chemotherapy

- There have been several prospective, randomized trials and large, single-arm studies that suggest that adjuvant chemotherapy given during and after radiation therapy may improve overall survival [29,30]. In the 1970s and 1980s, it was determined that there was a definite survival benefit for children with high-risk MB treated with postradiation chemotherapy with vincristine and lomustine (chloroethyl-cyclohexyl nitrosourea [CCNU]) [31]. A single-arm, limited institution study of radiation therapy with vincristine followed by CCNU and cisplatin chemotherapy demonstrated 5-year survival rates of approximately 85% for high-risk patients and approximately 90% 5-year survival rates for standard-risk patients [30,32••, Class II]. In another large, retrospective, single-center study, patients who received adjuvant chemotherapy had better outcomes compared with children who had received radiation alone; this study also identified one regimen (vincristine, lomustine, and cisplatin) that seemed to have better long-term control compared with other chemotherapy regimens [33•, Class II]. Chemotherapy is, therefore, now incorporated in most investigational studies for children with standard- and high-risk disease. The Children's Oncology Group is currently evaluating the results of a recently completed study, which examined the outcome and toxicities of a cyclophosphamide-based chemotherapy regimen compared with a CCNU-based regimen in children with standard-risk MB, and will build on these results with subsequent studies for standard-risk patients. A study is also in progress for patients with high-risk disease to determine whether further intensification of the chemotherapy regimen can lead to improved survival results.

Neoadjuvant (pre-radiation) chemotherapy

Studies on adjuvant chemotherapy are based on the premise that chemotherapy preceding radiation may be better tolerated because bone marrow supplies have not yet been stressed. It has also been suggested that cisplatin may have less ototoxicity if given before radiation therapy. Additionally, it has been hypothesized that chemotherapy may reduce tumor bulk and may make radiation therapy more efficacious. This approach was examined in the Children's Cancer Group 9931 and P9031 studies, as well as a number of institutional pilot studies. Although these studies demonstrated that it was feasible to give chemotherapy before radiation, in some instances it was found that chemotherapy-induced myelosuppression may have led to delayed commencement of radiation therapy [34]. To date, there has been no compelling evidence of a survival benefit to the use of pre-irradiation chemotherapy compared with more standard post-irradiation approaches, although long-term outcome analysis of the aforementioned cooperative group studies remains in progress.

Intrathecal chemotherapy

Intrathecal chemotherapy, or the delivery of chemotherapeutic agents directly into the CSF, is feasible, but response rates have not been impressive. In one study of five children with MB, there was no child with partial or complete response on neuroimaging, although clearance of tumor cells from CSF cytology was observed in two children [35]. The utility of intrathecal mafosfamide, in conjunction with intensive systemic chemotherapy, is currently being evaluated in the Pediatric Brain Tumor Consortium-001 study.

Radiation therapy

Craniospinal radiation

The traditional postsurgical radiation treatment for children with MB over 3 years of age has been 5400 to 5580 cGy to the tumor bed and approximately 3600 cGy to the entire neuroaxis. The minimal dose necessary to control disease is unknown. Because children younger than 3 years of age are particularly sensitive and susceptible to the adverse effects of radiation therapy on the immature developing brain, some studies have investigated the effects of delayed or reduced radiation in young children with MB [36–38]. Reduction of the craniospinal radiation therapy dose from 3600 to 2340 cGy has also been pursued in older children. Initially, concerns were raised in an intergroup study of this approach by the Pediatric Oncology Group and Children's Cancer Group that the lower dose of craniospinal irradiation had resulted in a significantly higher incidence of subarachnoid relapse of disease [38]. A recent update of that study showed a modest, but not statistically significant, difference in event-free survival between standard dose and reduced dose arms after 8 years of follow-up [39••, Class I]. Nonetheless, the nominally worse results with reduced dose therapy provided an impetus for the addition of chemotherapy in such patients. Preliminary studies suggested that reduced-dose radiation after surgery and adjuvant chemotherapy during and after radiation was feasible and may provide better overall outcomes for standard-risk MB patients than the use of standard-dose radiation alone [32••, Class II]. As noted, this approach has also been examined in the A9961 phase III study of the Children's Cancer Group and Pediatric Oncology Group (now known as the Children's Oncology Group). A planned follow-up study will test the feasibility of further reductions in the dose of craniospinal irradiation and in the volume of the posterior fossa boost.

Although radiation therapy dose reduction is being pursued for children with standard-risk disease, strategies for enhancing the efficacy of irradiation have been examined in those with high-risk tumors. These have included hyperfractionated radiation delivery (discussed later) and radiosensitization or chemoradiation. The recently completed P9631 study combined standard craniospinal irradiation with oral etoposide, an agent with known activity against leptomeningeal disease,

whereas the ongoing Children's Cancer Group 99701 study is administering carboplatin, a known radiosensitizer, during irradiation. These studies have incorporated the administration of additional chemotherapy on completion of irradiation.

Hyperfractionated radiation therapy

Hyperfractionated radiation therapy has been investigated as a means to reduce the side effects of radiation therapy while allowing an increase in total radiation dose. Prados *et al.* [40] reported 5-year survival data for low-risk MB patients treated with hyperfractionated radiation. There was no significant improvement in overall survival with hyperfractionated radiation therapy. This approach has also been examined in the Children's Cancer Group 9931 study, in conjunction with intensive pre-irradiation chemotherapy for patients with high-risk disease, although it remains uncertain whether the survival results will exceed those obtained with more standard approaches.

Conformal radiation therapy

New radiation therapy techniques have made it possible to "shape" the posterior fossa boost radiation dose to the contour of the tumor volume, rather than to the entire posterior fossa. Consequently, there is a lesser dose of radiation delivered to the peripheral brain tissue. This may prevent damage to the inner ear, proximal brain stem, and hypothalamopituitary axis. The rationale for this approach is supported by the fact that most MB recurrences are in the tumor bed or disseminated. Isolated relapses within the posterior fossa, but outside the tumor bed, are uncommon. It may be feasible to limit the boost dose to the tumor bed and margin. Although this approach has been examined in several institutional pilot studies, it remains to be determined whether disease control is equivalent to that obtained with standard boost volumes [41•, Class I]. To address this issue, the new Children's Oncology Group protocol for children with standard-risk MB will evaluate the feasibility and safety of delivering the posterior fossa boost dose of irradiation using three-dimensional conformal planning and delivery. The Children's Oncology Group will compare event-free survival and neurocognitive and endocrine outcomes in children who have received a boost dose of irradiation targeted strictly to the tumor bed plus a defined margin versus those who have received irradiation targeted to the entire posterior fossa.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) facilitates targeting of small tumor volumes with high-dose radiation therapy. Residual or recurrent disease may be treated with surgical resection or SRS before the administration of additional chemotherapy. However, it is still too soon to determine if radiosurgery will provide better survival outcomes compared with re-operation. In a recent study, it was shown that SRS offered limited benefit for patients with recurrent disease; six of 11 patients who underwent treatment for recurrent disease died. However, no patient failed locally and the predominant site of failure was distant within the CNS [42].

Recurrence of disease

- Unfortunately, recurrence of disease is common in children with MB. Disease at or near the initial tumor site, or even at a distant intra- or extra-axial location, may occur years after successful treatment. Secondary tumors may also develop and include meningiomas and glioblastoma multiforme. After detection of new or recurrent tumor, a complete and thorough staging must be performed. Biopsy or resection should be considered, especially if there is any question about the histology of a lesion. Palliative or definitive surgical resection may be considered. Although the prognosis for children with recurrent MB remains poor, long-term disease control has been

observed in some children using high-dose chemotherapy regimens with or without autologous stem cell rescue and observed occasionally after more conventional phase II chemotherapy [43–45].

Physical/speech therapy and exercise

- After surgical resection, children are often discharged to home or to inpatient rehabilitation therapy. There have been no prospective studies that demonstrate any benefit of one over the other. Each child is managed on an individual basis. Certainly, children with neurologic deficits should be offered physical, occupational, speech, and interventional therapy as needed. Once the family feels comfortable with the management of the child at home, and it is safe to discharge to home, the child may continue to receive outpatient therapy on a regular basis. Children who are in the process of receiving chemotherapy or radiation therapy may benefit from a "rest period," with resumption of therapy after the child has regained his or her strength.

Pediatric considerations

- Children younger than 3 years old have less favorable outcome compared with their older counterparts. There appears to be an increased incidence of dissemination at the time of diagnosis. Radiation therapy is often delayed in children under 3, because of the deleterious cognitive sequelae of radiation. Although the goal of chemotherapy in infants is to delay or reduce radiation therapy, only a fraction achieve long-term disease control with chemotherapy alone. Salvage radiation may be given to infants with recurrent disease, but there are significant cognitive losses associated with this treatment [46]. In an attempt to improve the survival rates for these infants, the Pediatric Brain Tumor Consortium has started a study to investigate the effects of intrathecal therapy plus limited field radiation therapy. After 20 weeks of systemic and intrathecal chemotherapy, the child receives conformal radiation therapy to the site of the initial tumor, followed by 20 weeks of systemic chemotherapy. The feasibility of this treatment and the event-free survival rates will be determined. There are several large studies that have investigated the treatment of infants with MB, including the Pediatric Oncology Group study 863, reported by Duffner *et al.* [47] and Heideman [48••, Class I] and the Children's Cancer Group 9921 study (whose manuscript is in preparation). Ongoing studies of the Children's Oncology Group are evaluating the use of a posterior fossa boost without full craniospinal radiation therapy followed by maintenance chemotherapy for infants with localized MB (P9934), as well as the use of intensive consolidation chemotherapy after initial induction therapy (Children's Cancer Group 99703). Their goal is improving the percentage of patients who experience long-term disease control.

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