

Management of and Prognosis With Medulloblastoma

Therapy at a Crossroads

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Medulloblastoma is the most common malignant childhood brain tumor and, although relatively uncommon in older patients, poses a therapeutic challenge in adults. With current means of therapy, children with nondisseminated medulloblastoma have a high likelihood of long-term survival; 80% or more will be alive 5 years after diagnosis and treatment, with many free of the disease. Even in children with disseminated disease, intensified therapy has been associated with improved survival rates, although some of this improvement may be more apparent than real. The quality of life in long-term survivors is a major issue, and most children who survive have substantial neurologic and cognitive sequelae. The outcome in infants and younger children with medulloblastoma is suboptimal, although there is some evidence to suggest that intensification of therapy has improved the likelihood of disease control. A better understanding of the biological characteristics of medulloblastoma including the cell or cells of origin and the aberrant cellular signaling pathways involved has the promise of dramatically changing tumor stratification and treatment in the near future. However, these biological advances have yet to be integrated into the treatment of medulloblastoma in children or adults.

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The treatment of medulloblastoma, the most common malignant tumor of childhood, is evolving.¹ The tumor occurs in patients of all ages, peaks in incidence in children between 3 and 9 years, is the most common malignant brain tumor in infants, and accounts for 1% to 2% of all brain tumors in adults.² Tumors in adults are most frequently diagnosed in the third and fourth decades of life. By definition, medulloblastomas arise in the posterior fossa, and histologically similar tumors originating from the pineal region or the cerebrum are no longer classified as medulloblastomas because there is increasing evidence that they are molecularly distinct from medulloblastoma.³ With the available means of treatment, there has been a reported increase in disease-free survival, overall survival, and possibly cure. However, changes in tumor stratification

and disease stratification may make some of these improvements more apparent than real, and the therapies required for treatment often have substantial detrimental effects on the quality of life in long-term survivors. The cell or cells of origin of medulloblastoma and the aberrant cellular signaling pathways involved in tumor growth have been better clarified in the last decade, leading to potential biologically based new forms of therapy.

CURRENT MANAGEMENT

The current management of medulloblastoma has evolved over the last 3 decades, primarily based on the results of prospective, multicenter, often randomized trials performed in children in North America and Europe. An integral part of all of these clinical trials has been the stratification of patients into risk groups.^{1,4} Since the late 1970s, two relatively distinct subsets of patients have been used after staging, primarily those with disseminated or residual postoperative primary-site disease (high- or poor-risk disease) and those with totally or near-totally resected nondisseminated tu-

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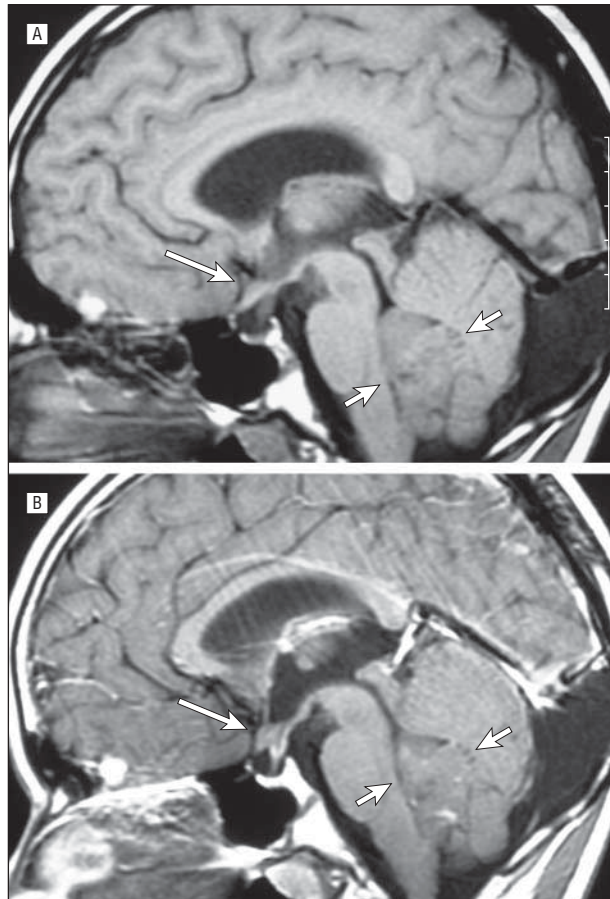


Figure. Sagittal T1-weighted images without contrast medium (A) and with contrast medium (B) in a child with a medulloblastoma. The tumor fills the fourth ventricle and shows minimal, punctuate enhancement (B). A nonenhancing metastasis is present in the infundibular recess of the third ventricle, causing abnormal thickening behind the chiasm. Arrows show the nonenhancing tumor and the infundibular metastasis.

mors (average-risk disease).^{1,4} Dissemination is determined by neuroimaging of the entire neuroaxis and cytologic analysis of the cerebrospinal fluid, preferably lumbar. Approximately 30% of patients with medulloblastoma will have evidence of disseminated disease at diagnosis, and in younger children, especially infants, the likelihood of disseminated disease is higher. Even in those without evidence of frank dissemination, because treatment with primary-site irradiation alone results only in disease control in less than 20% of patients, the standard therapy is craniospinal radiotherapy supplemented with local boost radiotherapy. Treatment with radiotherapy to the entire neuroaxis (36 Gy [to convert to rad, multiply by 100]) is associated with 5-year disease-free survival rates of 50% to 60% in patients with average-risk disease and 40% or less in patients with high-risk disease.^{1,4,6}

Means used to stratify patients have changed over time. In earlier trials stratification was based on findings at myelography and cerebrospinal fluid cytologic analysis. Over the last 2 decades, magnetic resonance imaging of the brain and spine, preferably performed preoperatively to prevent postsurgical artifacts, has supplanted myelography.^{1,4,7} Histologic analysis has been variably associated with outcome and has been used in some stratification schemes. The concept of an anaplastic medulloblas-

Table 1. Molecular Prognostic Parameters in Medulloblastoma

Neurotrophin-3-receptor ¹¹	Increased expression associated with improved survival
ERBB2 ¹²	Increased expression associated with poorer survival and metastasis
PDGFRA ¹³	Overexpression associated with metastasis
RAS/MAPK pathway ¹³	Overexpression associated with increased metastasis
MYCC/MYCN ¹⁴	Amplification and expression associated with poorer survival
γ - and β -Catenin ¹⁵	Expression associated with better survival
Survivin ¹⁶	Overexpression associated with better survival
p53 ¹⁷	Immunopositivity associated with poorer survival

Abbreviations: ERBB2, avian erythroblastosis oncogene B; MAPK, mitogen-activated protein kinase; MYCN, v-myc avian myelocytomatosis viral oncogene (OMIM 19008); PDGFRA, platelet-derived growth factor receptor, alpha polypeptide.

toma has been increasingly accepted, and current study in the United States and Canada is stratifying all patients with anaplastic tumors, independent of extent of disease or degree of resection, into the high-risk category.⁸ These changes in stratification have resulted in potential biases in the interpretation of more recent clinical studies that have altered therapy by changing the dosage or volume of radiotherapy and adding chemotherapy. With the use of magnetic resonance imaging as the primary staging technique and possibly altering trial assignment on the basis of histologic findings, some patients who would have been considered to have average-risk disease are being stratified as having high-risk disease. This has the potential effect that studies evaluating new forms of treatment will demonstrate improved rates of survival in children with both average- and high-risk disease without really changing outcome.

In addition, there is a substantial lack of uniformity and subjectivity in the stratification of patients on the basis of neuroradiographic and histopathologic findings. In 2 recent prospective studies in children with medulloblastoma, 1 performed in North America and the other in Europe, central neuroradiographic review disclosed inadequate neuroimaging or misinterpreted results in almost 20% of the cohort (**Figure**).^{9,10} Histopathologic analysis for anaplasia is highly subjective, and there are no uniformly accepted criteria for anaplasia because almost all medulloblastomas have some regions with anaplastic features. Furthermore, the differentiation of focal anaplasia from more severe or diffuse anaplasia is used in some classification systems, although this is a highly subjective, nonquantifiable distinction. A host of biological parameters have been identified in the past decade that have been associated with likelihood of tumor dissemination, anaplasia, disease-free survival, and overall survival (**Table 1**).¹¹⁻¹⁷ Attempts are ongoing to integrate these parameters into stratification schemes in the hope that this will enable more objective and refined determination of patient risk. However, most studies relating these biological parameters to survival have been retrospective, and results have been somewhat variable.

Table 2. Results of Selected Multicentered Trials in Children Older Than 3 Years With Medulloblastoma

Trial/Year	Eligibility	Treatment	Outcome
Thomas et al ¹⁸ /1986-1990	Nondisseminated disease (N=88)	CSRT, 23.4 vs 36 Gy	5 y: 67% ± 7% for CSRT at 36 Gy vs 52% ± 7% for 23.4 Gy CSRT at 23.4 Gy (<i>P</i> = .08); no difference in EFS at year 8
Kühl et al ⁶ /1991-1997	All stages (N=137)	Pre-RT CT vs post-RT CT (all, CSRT at 35 Gy)	PFS at 3 y: 84% ± 8% for post-RT vs 62% ± 9% for pre-RT in nondisseminated disease
Taylor et al ⁵	Nondisseminated disease (N=179)	Pre-RT CT vs RT alone (all, CSRT at 35 Gy)	Pre-RT plus CT 5-y EFS 74.2% vs no RT 5-y EFS 59.8%
Gajjar et al ¹⁹	All stages (N=134)	RT (CSRT at 24-44 Gy) plus CT and PSCR; 2400 for average-risk disease	5-y EFS 83% for average-risk disease vs 70% for high-risk disease
Packer et al ⁹	Nondisseminated disease (N=379)	CSRT at 23.4 Gy plus 1 of 2 during and after RT plus CT	5-y EFS 81% ± 2.1% for regimen A vs 86% ± 9% for regimen B

Abbreviations: CSRT, craniospinal radiotherapy; CT, chemotherapy; EFS, event-free survival; PFS, progression-free survival; PSCR, peripheral stem cell rescue; RT, radiotherapy.

It is unclear whether these parameters will supplant the clinical risk factors now used or will be used in combination with clinical findings to better assign disease risk.

TREATMENT IN CHILDREN OLDER THAN 3 YEARS, ADOLESCENTS, AND YOUNG ADULTS TO AGE 21 YEARS

Given the caveats about disease stratification, there is general consensus that the addition of chemotherapy to radiotherapy has significantly improved the rate of survival in children with medulloblastoma (**Table 2**).^{5,6,9,18,19} Studies in which chemotherapy was administered during and after radiotherapy with drug regimens such as cisplatin, *N*-(2-chloroethyl)-*N'*-cyclo-hexyl-*N*-nitrosourea (CCNU), and vincristine, or cyclophosphamide, cisplatin, vincristine, and etoposide have demonstrated survival rates as high as 85% in children with average-risk disease and 60% or better for those with poor-risk disease.^{9,17} Reported 5-year progression-free survival and overall survival in patients treated with radiotherapy alone have been remarkably consistent in studies performed over the last 25 years, at approximately 60%, including studies performed contemporarily with the radiotherapy plus chemotherapy trials.⁵ In a prospective randomized trial performed in the late 1980s that used radiotherapy alone, a reduction in the dose of craniospinal radiotherapy from 36 Gy to 24 Gy resulted in a higher incidence of early disease relapse in children with nondisseminated disease at diagnosis.¹⁸ Another smaller trial demonstrated disease control in only 40% of patients with average-risk disease if chemotherapy was used before reduced-dose (23.4 Gy) craniospinal radiotherapy.²⁰ The addition of chemotherapy during and after radiotherapy has allowed a reduction of the dose of craniospinal irradiation to 23.4 Gy, with excellent maintenance of disease control of greater than 80% at 5 years.⁹ The addition of chemotherapy to treatment regimens has also seemed to substantially decrease the likelihood of extraneural relapse and in preliminary analysis may have also decreased the likelihood of late (>5 years) disease recurrence.⁹ How much it has improved cognitive outcome is unclear; however, there is evidence to support a decrease in sequelae with lower dosages.

The timing of radiochemotherapy seems critical in disease control. In 2 randomized studies and other nonrandomized trials, preradiation chemotherapy has been as-

sociated with a poorer rate of control than treatment with immediate postoperative radiotherapy and concomitant chemotherapy.^{6,20} Although chemotherapy is a relatively standard component of treatment in children with both average- and high-risk disease, to our knowledge no well-powered definitive study comparing outcome in patients treated with radiotherapy with those treated with radiochemotherapy has been performed. Chemotherapy has additive toxic effects including cisplatin-related hearing loss, vincristine-associated neuropathy, a higher risk of life-threatening infections, hepatotoxicity, nephrotoxicity, and a possible decrease in long-term quality of life.^{1,4,5,9,21} Impressive survival results of 80% or greater in children with average-risk disease and greater than 60% in those with poor-risk disease have been reported after treatment with a higher dosage of postradiotherapy chemotherapy supported by peripheral stem cell rescue; however, it has not been demonstrated that such treatment is superior to less aggressive regimens.^{9,19} Potential benefits of these higher-dosage regimens include truncation of therapy and a possible decrease in exposure to potentially neurotoxic therapy such as cisplatin.

TREATMENT IN ADULTS

Because there are few adults with medulloblastoma, prospective comparative therapy trials are limited. In general, as has been documented in adolescents, young adults have difficulty tolerating the agents used in pediatric studies.²² Cisplatin results anecdotally in more dose-limiting peripheral neuropathy in adults than in children. The peripheral neuropathy after vincristine therapy is more severe, or at least less well tolerated, in older patients than in children younger than 12 years.²² For these and other reasons, delivery of the same intensity of drug therapy used in pediatric trials to adults has been difficult, if not impossible. While there is no evidence that adults with medulloblastoma, who in general are less likely to have disseminated disease at diagnosis, benefit from the addition of chemotherapy to radiotherapy, the reported series to date have been small and often retrospective and underpowered.²³⁻²⁵ Survival rates in adults have been in the range of 50% to 60%, similar to that in children treated with radiotherapy alone and seemingly inferior to that in patients younger than 21 years receiving adjuvant radiotherapy and chemotherapy.^{1,4}

TREATMENT IN INFANTS AND YOUNG CHILDREN

The management of medulloblastoma in infants is highly problematic and suboptimal.^{1,4,26,27} Owing to the high likelihood of severe neurocognitive damage secondary to whole-brain irradiation delivered as part of craniospinal radiotherapy, most efforts over the last 2 decades have focused on use of chemotherapy in children younger than 3 years, and in some studies, younger than 5 years, either to delay or obviate the need for radiotherapy.²⁶⁻²⁸ Results of such an approach have been mixed. Early studies using drug combinations such as cyclophosphamide, cisplatin (*cis*-diamminedichloroplatinum), vincristine sulfate, and etoposide phosphate demonstrated that approximately 40% or less of patients younger than 3 years could be successfully treated with chemotherapy until they reached age 3 years, followed by craniospinal irradiation.²⁶ Primarily, those children with extensively resected nondisseminated tumors survived, and in those who survived, craniospinal irradiation delivered at age 3 years likely caused permanent cognitive damage. Subsequent studies attempted to intensify chemotherapy and not use craniospinal irradiation. These studies intensified chemotherapy by increasing drug dosage, with or without peripheral stem cell support, or adding other chemotherapeutic agents including intrathecal agents, and demonstrated possible improvements in progression-free survival, although other factors may also be responsible for this apparent improvement.^{27,28} Approximately 15% to 20% of infants who would previously have been diagnosed as having medulloblastoma harbor a different embryonal tumor, the atypical teratoid/rhabdoid tumor.²⁹ This tumor, which can be reliably diagnosed on the basis of immunohistochemical and molecular genetic findings, is associated with an extremely poor prognosis, with few, if any, infants surviving with currently available treatments. The removal of this subset of patients from the medulloblastoma study population will improve reported survival outcomes.

In one study in which both intrathecally and intravenously administered methotrexate sodium were used in addition to more standard chemotherapeutic agents, more than 50% of patients were free of disease after treatment with chemotherapy alone.²⁸ The subgroup with the best prognosis included those with the histologic desmoplastic variant.²⁸ Unpublished retrospective reviews have found the desmoplastic variant of infant medulloblastoma in 30% to 60% of infants with the disease, and in those with desmoplastic tumors, a markedly improved rate of survival was noted after chemotherapy compared with that in patients harboring the more classic medulloblastoma. The presence of desmoplasia or other specific molecular markers connotes a better prognosis in a subgroup of patients, with a high likelihood of long-term disease control after chemotherapy alone.^{11,15,28} Thus, it is unclear to what degree the improved survival is the result of the intensified drug regimens, including those using high-dose chemotherapy with peripheral stem cell rescue, rather than a by-product of inadvertent selection bias. There is also little question that the more intensive regimens place children at higher risk for sequelae, be they regimens that

use high-dose chemotherapy supplemented with peripheral stem cell rescue or those that have integrated methotrexate, a drug with potential neurotoxic reaction. In the group of infants with nondesmoplastic nondisseminated medulloblastoma, trials are under way that couple chemotherapy with local radiation therapy. The prognosis of medulloblastoma in infants younger than 3 months with nondesmoplastic disseminated disease is particularly poor, with less than 20% surviving 5 years after diagnosis.²⁸

LONG-TERM SEQUELAE

Long-term neurologic, endocrinologic, and neurocognitive sequelae are well documented in medulloblastoma survivors.³⁰⁻³⁴ Although cranial irradiation has been considered the primary cause of sequelae, other factors such as preoperative neurologic status, the effect of concomitant hydrocephalus, the use of chemotherapy, and perioperative complications have also been implicated. In recent prospective international studies, as many as one-fourth of all patients developed posterior fossa mutism syndrome after surgery.³⁵ Initially considered a rarity, this condition, manifested by an apparent delayed onset of mutism, usually 6 to 24 hours after surgery, and associated with variable degrees of cerebellar dysfunction, axial hypotonia, supranuclear cranial nerve palsies, and severe emotional lability, has been reported in almost 25% of more than 500 children treated in recent prospective studies. The etiology of the syndrome is undetermined, although increasing evidence suggests that it is the result of cerebellar vermal damage and possible disruption of the dentatorubrothalamic connections to the supplementary motor cortex. It is unclear why this syndrome is being diagnosed more frequently; however, it seems likely that this is the result of a change in operative techniques rather than just poor recognition in the past. Approximately 50% of patients with symptoms of posterior fossa mutism syndrome will have long-term neurologic deficits. Although speech returns in most patients, it is often abnormal, and patients are at increased risk of permanent neurocognitive sequelae.³⁵

Whole-brain irradiation has been implicated as a significant cause of intellectual deterioration in patients of all ages, and the effect on global intelligence is clearly greater in younger children.^{30,31} After 36 Gy of cranial irradiation, children treated at age 3 to 7 years are likely to have a 20- to 30-point decrease in overall intelligence. Even after reduced-dose craniospinal irradiation of 24 Gy, now used widely in patients with nondisseminated disease, a decrease of 10 to 15 points or more is expected within 2 to 3 years. Older patients, while not usually demonstrating as large a decrease in overall intelligence, commonly demonstrate selective learning disabilities. The types of cognitive disabilities are variable and include deficits in learning, executive function, attention, and memory. The additive role, if any, of primary-site irradiation to the posterior fossa in the cause of these deficits is poorly elucidated. Chemotherapy may cause additional sequelae such as ototoxic effects related to cisplatin therapy. In a recent review, those children who received chemotherapy in addition to radiotherapy had lower scores on a quality-of-life assessment than did those who received radio-

therapy alone.²¹ Host vulnerabilities, probably genetic, that likely have a major role in determining the severity of deficits that develop, have yet to be elucidated.

MOLECULAR BIOLOGY AND THE FUTURE

The rapid increase in the understanding of the molecular biology of medulloblastoma suggests the possibility that therapy in the future can be tailored and, it is hoped, improved on the basis of an individual tumor's molecular genetic composition. As recently as a decade ago, the cellular origins of medulloblastoma were essentially unknown.^{1,4} A convergence of evidence from different lines of neurobiological and neuro-oncologic investigations, as well as a better understanding of the genetic underpinnings of syndromes associated with a higher incidence of medulloblastoma such as Gorlin syndrome (nevoid basal cell carcinoma) and Turcot syndrome, has suggested that specific molecular genetic abnormalities and cellular signaling pathways are integral in medulloblastoma development and progression.^{3,4,8,12-14,36} A detailed discussion of these molecular genetic pathways is beyond the scope of this review; however, one theory based on these discoveries suggests that medulloblastoma arises from 1 of the 2 germinal zones of the cerebellum: the ventricular zone and the external granular layer.³⁶ Although there is substantial molecular overlap between embryonal cells in these 2 germinal zones of the cerebellum, the more laterally positioned external granular layer has a more restricted neuronal progenitor cell pool. Desmoplastic medulloblastomas, which in general are more likely to arise laterally in the posterior fossa, frequently demonstrate markers of granular cell lineage and are believed to arise predominantly from this neuronally restricted pool of cells. Tumors in patients with Gorlin syndrome are predominantly desmoplastic and seem to be associated with a more favorable prognosis.³⁶⁻³⁸ Similarly, infants with desmoplastic tumors fare better than those with classic medulloblastomas. Gorlin syndrome is caused by an inherited germline mutation of the *PTCH* (patched homolog 1) gene (OMIM 601309) on chromosome 2. The *PTCH* gene is an inhibitor of sonic hedgehog signaling, and sonic hedgehog signaling has been implicated in 10% to 20% of medulloblastomas. In a mouse model, tumors with this molecular alteration have regressed after treatment with sonic hedgehog pathway antagonists.³⁷

The signaling pathway underlying Turcot syndrome, which is associated with a germline mutation in the *APC* (adenomatous polyposis coli) gene (OMIM 601309) and is associated with a higher incidence of medulloblastoma, involves the Wnt (wingless-type mouse mammary tumor virus integration site family member) (OMIM 1648290) pathway.³⁹ Abnormalities in the Wnt signaling pathway, mutated in as many as 15% of medulloblastomas, have been associated with a high likelihood of long-term survival, and this pathway is another therapeutic target.^{15,39}

The multipotential progenitor cells of the ventricular germinal matrix of the cerebellum may be the cell of origin for the more common classic midline medulloblastoma.³⁶ Targeted therapy with agents aimed at molecular genetic abnormalities that are likely to be present in classic medulloblastoma, such as increased expression

of cell surface growth factor receptors including epidermal growth factor, platelet-derived growth factor, or platelet-derived growth factor ERBB2, and upregulation of downstream components of signal transduction such as the RAS-MAP (mitogen-activated protein kinase 1) (OMIM 176948) kinase pathways are being studied.^{4,12,13}

Although identification of the specific molecular genetic abnormalities in patients with medulloblastoma is useful, in stratification of patients, at least retrospectively; the use of agents to antagonize specific growth pathways or disrupt downstream messengers has not yet shown efficacy in limited clinical trials. It is unclear how these molecular targeted agents should be best integrated into therapy. Because of the complexity of cellular signaling and the multiple escape pathways present to overcome individual signaling inhibitors, it may be best to couple them with radiotherapy or chemotherapy or to use these agents as a biological cocktail, hitting multiple targets simultaneously. Retinoic acid, based on the observations that tretinoin (all-*trans* isomer) and isotretinoin (13-*cis*-retinoic acid) inhibit growth of medulloblastoma cell lines and induce apoptosis and neuronal differentiation, is in clinical trials coupled with radiotherapy and chemotherapy.⁴⁰ Similarly, there is considerable enthusiasm in adding ERBB2 and platelet-derived growth factor receptor, alpha polypeptide antagonists to conventional chemotherapy and radiotherapy.

CONCLUSIONS

The understanding and management of medulloblastoma is evolving. In certain subsets of patients, survival has improved with the addition of chemotherapy to postoperative radiotherapy. In other subsets of patients, especially infants and those with widely disseminated disease, although there may be a somewhat higher likelihood of disease control with more aggressive treatments, therapy remains suboptimal. The therapies currently required for disease control result in an inordinately high and unacceptable rate of transient and permanent sequelae. Although it is possible that modifications of currently available therapies may improve survival in some children with medulloblastoma, it seems unlikely that alterations in the type and extent of standard chemotherapeutic agents or radiotherapy now in use are unlikely to result in dramatic improvement in survival or a decrease in long-term deficits. Molecular-targeted therapies are being studied in patients with medulloblastoma and hold great promise. However, a substantial amount of work is needed to determine which agents should be used and how they are best used.

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