Medulloblastoma
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What is This?
Medulloblastoma is the most common malignant brain tumor in children. Patients with medulloblastoma are stratified into “standard” and “high” risk categories based on age at diagnosis, degree of surgical resection, and disease spread. In children older than 3 years of age, the long-term survival can be achieved in approximately 85% of standard risk patients and 70% of high risk patients with a combination of chemotherapy and irradiation. Younger children, particularly infants, are at a significantly higher risk of side-effects of treatment. Despite tremendous progress in the field of molecular biology of medulloblastoma, much remains to be achieved in understanding the pathogenesis, critical pathways responsible for medulloblastoma, and molecular risk stratification, and in devising treatment strategies with even better survival and less long-term sequelae.

Keywords: medulloblastoma; treatment and late effects; notch; sonic hedgehog; wingless

Medulloblastoma is a highly malignant embryonal tumor or primitive neuroectodermal tumor of the cerebellum with propensity for leptomeningeal dissemination. It is classified as a World Health Organization (WHO) grade 4 tumor. Dr James Wright first described a tumor in the cerebellum that resembled neuroblastoma in 1910 and called it a neurocytoma.1 The term medulloblastoma was first coined in 1925 by Bailey and Cushing, who described the tumor as a highly malignant glioma arising in the fourth ventricle and noted its tendency to spread to other parts of the central nervous system.2 Approximately 75% of medulloblastomas occur in midline, and hemispheric location is associated with older age and desmoplastic histology. Most patients present with signs and symptoms of increased intracranial pressure and incoordination. Risk stratification for patients is based on age, degree of surgical resection, and disease spread. Surgery and chemotherapy are the mainstay of therapy for medulloblastoma in all age groups. Radiation therapy is used mainly for patients who are older than 3 years of age. A large majority of patients greater than 3 years of age with nondisseminated medulloblastoma can now be cured with a combination of these 3 modalities but not without significant side-effects related to the treatment and tumor itself. A significant proportion of the high-risk patients (infants, disseminated disease at diagnosis, and patients with anaplastic medulloblastoma) will still relapse from the disease, despite aggressive therapy. This review will provide an overview of epidemiology, clinical presentation, pathology, radiological diagnosis, molecular biology, pathogenesis, risk stratification and treatment of “standard risk,” “high-risk,” and infant medulloblastoma.

Epidemiology

Medulloblastoma is the most common malignant brain tumor in children and accounts for approximately 20% of all pediatric central nervous system tumors and 40% of all posterior fossa tumors.3 The incidence of medulloblastoma in patients 0 to 19 years of age is 0.6 per 100 000 person-years, according to the Central Brain Tumor Registry of the United States 2008 report.3 The peak incidence of medulloblastoma is between 5 and 7 years of age with 10% of cases diagnosed within the first year of life, and the incidence decreases with age. Approximately 30% of all medulloblastomas occur in children older than 10 years of age and account for less than 1% of all brain tumors in adults.3 Medulloblastoma is 1.85 times more common in whites than blacks and 1.6 times more common in males than in females.3

Clinical Presentation

The clinical findings depend on the age of the patient and extent of their disease (local vs disseminated). The most
common signs and symptoms of medulloblastoma are a consequence of raised intracranial pressure from obstructive hydrocephalus, such as excessive irritability, vomiting, setting sun sign and increasing head circumference (often seen in infants), headaches, vomiting, diplopia, nystagmus, ataxia, and papilledema. The headaches are usually the first symptom in older children. The headaches get worse when the patients are lying down and are present when patients wake up in the morning, and there is often some relief with vomiting. Pressure on the dorsal midbrain from obstructive hydrocephalus can cause a cluster of findings known as Parinaud syndrome. In this syndrome, patients have upward gaze palsy and their pupils react to accommodation but not to light. Midline cerebellar tumors can cause truncal ataxia and unsteady gait, whereas tumors in the cerebellar hemispheres may cause appendicular ataxia and dysmetria. In addition, patients with disseminated disease can also present with clinical findings related to the sites of metastatic disease, such as signs and symptoms of cord compression from spread to the spinal cord or seizures from dissemination to the cerebral hemispheres.

### Diagnosis

Diagnosis is usually made on a computed tomography (CT) scan either when the patient first presents in the emergency department or to their primary provider who orders this scan. On CT scan, medulloblastoma appears as a midline, solidly enhancing, and homogeneous mass in the posterior fossa. Cystic changes and calcifications can also be seen but infrequently. The diagnosis of a posterior fossa mass is confirmed by magnetic resonance imaging (MRI), and medulloblastomas appear as hypointense on T1-weighted images, hypointense on T2-weighted images, and heterogeneously contrast enhancing on postgadolinium images. Leptomeningeal disease in the spinal cord and other parts of the brain is usually contrast enhancing and gives a "sugar coated" appearance. Magnetic resonance imaging of the spine should be performed at diagnosis along with the MRI of the brain for staging, whenever possible. If MRI of the entire spine is not performed at diagnosis, it should be performed approximately 10 to 14 days postoperatively, because the blood products or tissue debris could be misinterpreted as tumor nodules in the immediate postoperative period. Similarly, a lumbar puncture should also be performed 10 to 14 days postoperatively because of the risk of a false-positive result from tumor spill in the immediate postoperative period. Magnetic resonance imaging of the spine should be performed prior to the lumbar puncture, if possible, because blood from a traumatic lumbar puncture in the spinal canal can give a false appearance of drop metastases.

Magnetic resonance spectroscopy is also being increasingly used in the clinical management of medulloblastoma patients. Magnetic resonance spectroscopy helps distinguish between postirradiation necrosis from tumor progression. Magnetic resonance spectroscopy is used to assess the absolute concentration of various chemicals within the tumor tissue. For example, high choline concentration indicates high turnover of tumor cells as it is a proliferation marker for biomembranes; N-acetylaspartate is a neuronal marker and it is reduced within the tumor tissue. Neoplasms typically have a high choline concentration and reduced N-acetylaspartate, thus a high choline-to-N-acetylaspartate ratio. Radiation necrosis, however, would have a low choline peak and somewhat preserved N-acetylaspartate. It has recently been reported that absolute concentration of taurine is elevated on magnetic resonance spectroscopy, and this finding can be used to distinguish medulloblastoma from other tumors in the posterior fossa (Figure 1). Increased uptake has been reported on [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans in patients with medulloblastoma and has been shown to be negatively associated with survival.

### Pathology

According to the 2007 WHO classification of the tumors of the central nervous system, medulloblastoma has been classified as classical medulloblastoma, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, and large cell medulloblastoma. On histopathology, classical medulloblastomas are composed of sheets of small, blue, round cells with high nucleus-to-cytoplasm ratio and with abundant mitoses. Homer-Wright rosettes or pseudorosettes can be seen occasionally. Glial differentiation or necrosis can be seen in a minority of cases. Desmoplastic variant of medulloblastoma is more commonly seen in patients with Gorlin syndrome and occurs more often in cerebellar hemispheres of older children and adults. It is characterized by pale nodular areas that are surrounded by densely packed tumor cells along with a rich reticulin network. The nodular areas represent more mature areas of the tumor with cells having more cytoplasm and low rate of mitoses. This subtype has been shown to have a better prognosis when compared with classical medulloblastoma.

In large cell/large cell anaplastic tumors, the cells display significant nuclear pleomorphism, prominent nucleoli, and abundant mitoses. This subset of medulloblastoma has been reported to occur in approximately 4% of tumors. Medulloblastoma with myogenic and melanotic differentiation has also been reported and described as medullomyoblastoma and melanocytic medulloblastoma, respectively. In medullomyoblastoma, there is a spindle
cell population mixed with the tumor cells, which are positive for desmin and myoglobin. Melanocytic tumors have cell population that may test positive for S-100 and have been shown to accumulate pigment resembling melanin on electron microscopy.\textsuperscript{14,15}

On immunohistochemistry, a majority of medulloblastoma cells express neuronal markers, such as Protein Gene Product 9.5, neurofilament, neuron-specific enolase, and synaptophysin. Occasionally, there are cells that express glial fibrillary acidic protein (GFAP).\textsuperscript{16,17} Different subtypes of medulloblastoma are shown in Figure 2.

### Congenital Cancer Syndromes, Pathogenesis, and Signaling Pathways

Some of the information about the molecular pathways involved in medulloblastoma comes from its association with 2 congenital cancer syndromes: Gorlin syndrome and Turcot syndrome.

#### Sonic Hedgehog Pathway

Gorlin syndrome, or nevoid basal cell carcinoma syndrome, is an autosomal dominant condition in which patients develop basal cell carcinomas, multiple skeletal anomalies, and macrocephaly. Approximately 3\% to 5\% of patients develop medulloblastoma, mainly desmoplastic medulloblastoma. Patients with this syndrome have been shown to have a germline mutation at chromosome 9q22.3.\textsuperscript{18} The gene identified in this region and thought to be responsible for this syndrome is the Patched 1 (\textit{PTCH1}) gene, the human homolog of the Drosophila patched gene.\textsuperscript{19}

Patched 1 is a transmembrane protein, which functions as the receptor for sonic hedgehog.\textsuperscript{20} Sonic hedgehog signaling pathway plays a very important role in the early development of cerebellum. It has been hypothesized that the cerebellum develops from the granule precursor cells that migrate from the roof of the fourth ventricle to form the external granular layer of the cerebellum under the influence of sonic hedgehog produced by the Purkinje neurons present underneath the external granular layer. Once in the external granular layer, these precursors divide and postmitotic neurons move eventually to the internal granular layer. Sonic hedgehog has also shown to be responsible for proliferation of the external granular layer precursor cells.\textsuperscript{21,22}

The Patched receptor associates with another protein called smoothened.\textsuperscript{20} Smoothened in turn activates the release of glioma-associated oncogene homolog 1, a transcription factor, from a complex consisting of proteins such as fused and suppressor-of-fused. Patched functions to suppress signaling by smoothened. Once sonic hedgehog binds to Patched, it releases the inhibitory influence that Patched has over smoothened and thus increases the level of glioma-associated oncogene homologue in the cytoplasm, which in turns translocates to the nucleus and activates the transcription of various genes.\textsuperscript{23} Mutations in the \textit{PTCH} gene have been described in approximately 10\% to 15\% of sporadic medulloblastomas.\textsuperscript{22,24,25} Less commonly, mutations have also been described in sonic hedgehog, smoothened, and fused and suppressor-of-fused in patients with medulloblastoma.\textsuperscript{26-28}

#### Wingless Pathway

The involvement of Wingless pathway in medulloblastoma is suggested by patients with Turcot syndrome with
medulloblastoma and mutations in the adenomatous polyposis coli (APC) gene. In Turcot syndrome, the patients develop colorectal adenomas and medulloblastomas and have germ line mutations in the APC gene. Patients with Turcot syndrome have a 92-fold higher relative risk of developing medulloblastomas.

Adenomatous polyposis coli exists in the cytoplasm in a complex with other proteins, such as glycogen synthase kinase 3, axin 1, axin 2, β-catenin, and protein phosphatase 2A. The role of adenomatous polyposis coli complex is to control the level of β-catenin in the cytoplasm by causing its degradation. The adenomatous polyposis coli complex is in turn regulated by the cell membrane receptor protein called Frizzled. The Wingless pathway is activated when Wingless binds to Frizzled and activates it. Frizzled then phosphorylates the downstream target protein, dishevelled. Dishevelled then inhibits the proteins in the adenomatous polyposis coli complex resulting in accumulation of β-catenin in the cytoplasm. β-catenin then translocates into the nucleus and activates the transcription of various oncogenes, such as c-myc and cyclin D1. Mutations in the β-catenin gene and other genes of Wingless pathway have been described in 10% to 15% of sporadic medulloblastoma.

**Notch Pathway**

Notch signaling is activated by 4 transmembrane receptors—Notch 1, Notch 2, Notch 3, and Notch 4. The receptors are each made up of an extracellular domain and an intracryptoplasmic domain. After binding of the ligand to the extracellular domain, the protein undergoes double proteolytic cleavage, the first cleavage mediated by a metalloprotease and occurring at the external surface of the cell membrane and the second cleavage mediated by a γ-secretase complex at the intracellular portion of Notch. This results in the release of the intracellular domain into the cytoplasm, which translocates into the nucleus and activates transcription of various downstream targets, such as cyclin D1 and apoptosis related genes. Notch 1 and Notch 2 have been implicated in the development of normal
cerebellum and Notch 2 has been shown to be overexpressed in approximately 15% of all medulloblastomas.\textsuperscript{35,36}

**Epidermal Growth Factor Receptor (EGFR) Pathway**

The epidermal growth factor receptor family of receptor tyrosine kinases (also known as Erb due to their homology to the avian erythroblastosis virus), includes ErbB1, ErbB2, ErbB3, and ErbB4. These proteins exist as dimers on the cell surface. These receptors dimerize upon ligand binding. Dimerization produces a conformational change in the intracytoplasmic portion or the tyrosine kinase portion of the protein, which causes these proteins to cross-phosphorylate each other at tyrosine residues and become activated. These, in turn, phosphorylate various downstream targets and signaling pathways, including the Ras/Raf pathway, signal transducers and activators of transcription pathway, Akt pathway and mitogen-activated protein kinase pathway, which control various cellular functions, such as apoptosis, differentiation, proliferation, and survival.\textsuperscript{37} Of the medulloblastoma tumor samples, 80% have been shown to overexpress ErbB2, and its overexpression has been associated with a worse outcome in some studies.\textsuperscript{38,39}

**Risk Stratification in Medulloblastoma**

Currently, medulloblastoma risk stratification is based on age (less than or greater than 3 years of age), presence or absence of disseminated disease based on MRI findings and cerebrospinal fluid cytology (Chang classification system), or extent of resection. Magnetic resonance imaging of the brain and spine with and without contrast and cerebrospinal fluid evaluation for malignant cells is used for staging disseminated disease. Lumbar cerebrospinal fluid and not ventricular cerebrospinal fluid cytology is used for staging.

In the modified Chang staging system for medulloblastoma, M0 stage is assigned to patients with no evidence of tumor dissemination on brain and spine MRI, M1 stage is assigned to patients in whom only cerebrospinal fluid cytology is positive with a negative brain and spine MRI, M2 patients have macroscopic dissemination on the brain MRI and a negative spine MRI, M3 disease patients have macroscopic spinal metastases, and in M4 stage there is extraneural spread to distant organs, such as bones.\textsuperscript{40} Diffuse anaplasia on histology has also been shown to be a worse prognostic factor in children older than 3 years of age.\textsuperscript{41,42} Younger age (less than 3 years of age) is associated with worse prognosis, probably because the tumors are more extensive at presentation and difficult to operate upon, and because of the inability to use irradiation as a treatment modality. Survival figures for different prognostic groups are shown in Figure 3.

Patients with medulloblastoma are classified as being standard risk, if they are older than 3 years of age and there is no evidence of neuraxis dissemination on brain and spine MRI and lumbar cerebrospinal fluid, no evidence of extraneural spread to other organs, and less than 1.5 cm\(^2\) of residual tumor on the postoperative MRI scan. The high-risk patients are defined as having disseminated disease on brain and/or spine MRI, positive cerebrospinal fluid cytology, incomplete or partial resection of the primary tumor (greater than 1.5 cm\(^2\) residual on postoperative MRI scan), and anaplastic histology.\textsuperscript{43}
Molecular Prognostic Factors

In addition to the clinical factors, a variety of molecular markers have also been found to have a prognostic significance in medulloblastoma. When investigators from Germany looked at molecular risk factors in 113 medulloblastoma patients more than 3 years of age at diagnosis enrolled on the German HIT’91 trial, high Trk C expression and c-myc mRNA expression were found to be associated with a favorable prognosis in multivariate analysis.\(^3\) In another study from St Jude Children’s Research Hospital, 40% of medulloblastomas were found to overexpress ERBB2, more commonly large cell anaplastic tumors, and it was associated with a worse prognosis. Trk C, c-myc, and n-myc were not found to be of any prognostic value in this study, however.\(^3\) Ellison et al reported the results from the International Society of Pediatric Oncology and United Kingdom Children’s Cancer Group Primitive Neuroectodermal Tumors-3 trial in which they tested the prognostic value of nuclear β-catenin immunohistochemical staining on 109 medulloblastoma samples. Five-year overall survival and event-free survival were 92.3% and 88.9% for patients with positive nuclear β-catenin staining versus 65.3% (95% CI, 54.8% to 75.7%) and 59.5% for patients with negative nuclear β-catenin staining, respectively. Overexpression of survivin, an inhibitor of apoptosis, by immunohistochemistry, was tested on 56 medulloblastoma samples. Survivin expression was found to be an independent negative predictive factor.\(^\text{45}\) These molecular factors will play an important role, along with clinical risk factors, in risk stratification of medulloblastoma patients in the future.

Treatment

The treatment of medulloblastoma includes surgery, chemotherapy, and irradiation. The role of surgery and irradiation has been recognized since the first reported case of medulloblastoma in 1925 by Cushing and Bailey.\(^2\) The main site of failure in these patients was the leptomeninges in the brain and spinal cord. In a report of 22 cases of medulloblastoma by Cuneo and Rand in 1952, 13 patients received radiotherapy and their survival ranged from 4 to 30 months as compared to 5 days to 4 months for patients not treated with irradiation. None of these patients had a gross total resection of their primary tumor.\(^4\)

The treatment of children with medulloblastoma can be divided into 3 main categories: standard risk medulloblastoma in patients older than 3 years of age, high-risk medulloblastoma in patients older than 3 years of age, and medulloblastoma in infants and young children.

Treatment of Standard Risk Medulloblastoma Patients Older Than 3 Years of Age

In a study conducted by the Children’s Cancer Group and the Radiation Therapy Oncology Group for children with standard risk medulloblastoma more than 3 years of age (Children’s Cancer Group 942), 233 patients were randomized to receive either full-dose craniospinal irradiation to 36 Gy with a posterior fossa boost to 54 Gy alone or similar irradiation dose but with prednisone; cisplatin, vincristine, and lomustine; and vincristine chemotherapy. The 5-year progression-free survival was 50% for the irradiation arm versus 59% for the irradiation and chemotherapy arm, and the 5-year overall survival was 65% for both groups.\(^4\) This difference was not statistically significant. This study did not suggest a role for chemotherapy in patients with standard risk medulloblastoma or maybe the lack of a role for prednisone; cisplatin, vincristine, and lomustine; and vincristine chemotherapy in medulloblastoma.

In a combined Children’s Cancer Group (923) and Pediatric Oncology Group (8631) study, patients 3 to 21 years of age with standard risk medulloblastoma were randomized to receive either full-dose craniospinal (craniospinal irradiation, 36 Gy) or reduced-dose craniospinal irradiation (23.4 Gy) followed by a posterior fossa boost.

The protocol was terminated prematurely because of early relapses in the reduced-dose craniospinal irradiation arm. However, on longer follow-up, the 5-year progression-free survival was 67% in the full-dose craniospinal irradiation arm and 52% in the reduced-dose craniospinal irradiation arm (\(P = .80\)).\(^4\) Mulhern et al\(^4\) reported on the neuro-psychologic outcome for 22 children treated on this study. At a median time of 8 years from diagnosis, patients had a median Full-Scale IQ of 82.9. Children who were younger than 8 years of age at diagnosis and received 23.4 Gy craniospinal irradiation (median Full-Scale IQ = 70 for 6 children) had a 10 to 15 IQ point advantage when compared to children receiving full-dose craniospinal irradiation to 36 Gy (median Full-Scale IQ = 85 for 5 children).\(^4\)

To further address the role of reduced-dose craniospinal irradiation in children with medulloblastoma, Packer et al, treated 63 children greater than 18 months of age with irradiation (36 Gy craniospinal irradiation and posterior fossa boost for patients with high-risk disease and 23.4 Gy craniospinal irradiation and posterior fossa boost for patients less than 5 years of age and with standard-risk disease) and chemotherapy with vincristine; cisplatin, vincristine, and lomustine; and cisplatin. The 5-year progression-free survival for the entire group was 85% + 6%. The 5-year progression-free survival was 67% + 15% for patients with metastatic disease and 90% + 6% for patients with localized disease at the time of diagnosis (\(P = .037\)).\(^5\)

Children’s Cancer Group tested the feasibility of this strategy in a national study for patients between 36 months
and 120 months of age with standard risk medulloblastoma (9892). Patients were treated with reduced-dose craniospinal irradiation (23.4 Gy) with posterior fossa boost and chemotherapy with eight 6-week cycles of cisplatin, vincristine, and lomustine. The 5-year progression-free survival was 79% + 7% for all patients. These results supported the use of reduced-dose craniospinal irradiation along with adjuvant chemotherapy for patients with non-disseminated medulloblastoma.

When the intellectual outcome results were reported on 43 patients enrolled on Children’s Cancer Group 9892 protocol, the predicted Full-Scale IQ had dropped from 96.2 at baseline (95% CI: 90% - 102%) to 78.8 (95% CI: 71.4% - 86.3%) 4 years after completion of radiation therapy. The predicted rate of decline was 4.3 points per year for Full-Scale IQ, 4.2 points for Verbal IQ and 4 points per year for nonverbal IQ. Females were affected more than males ($P = .08$) and children younger than 7 years of age were affected more than older children ($P = .016$). Finally, the patients with baseline IQ score $>100$ suffered greater declines in IQ than those with baseline IQ scores of $<100$ ($P < .011$). This study suggested that although the loss of intelligence was less severe with reduced dose irradiation, it was still significant.

The Children’s Oncology Group study then undertook a phase 3 study to see whether a cyclophosphamide-containing regimen instead of cisplatin, vincristine, and lomustine following reduced-dose craniospinal irradiation (23.4 Gy) with posterior fossa boost with concurrent vincristine would increase the rate of progression-free survival in children with standard risk medulloblastoma. Four hundred and twenty-one patients with standard risk medulloblastoma between 3 and 21 years of age were enrolled on this study. The 5-year progression-free survival and overall survival for the entire cohort of 379 evaluable patients were 81.9% + 2.1% and 86% + 9%, respectively. There was no significant difference in progression-free survival and overall survival between the 2 treatment arms. Interestingly, more grade 4 hematologic toxicity and infections occurred on the cyclophosphamide-containing regimen and poor performance score in patients treated on cisplatin, vincristine, and lomustine-containing regimen. Among various prognostic factors that were evaluated, only excessive anaplasia was associated with a slightly worse prognosis (5-year progression-free survival of 83% vs 73% and 5-year overall survival of 89% vs 75%). The results of the neurocognitive testing of the patients on this study have not yet been reported.

Due to significant long-term side-effects of irradiation on young children, a pilot study of 10 nondisseminated medulloblastoma patients younger than 5 years of age, diagnosed between 1988 and 1990, was performed using 18 Gy craniospinal irradiation and posterior fossa boost to 50.4 to 55.8 Gy with concomitant weekly vincristine followed by eight 6-week cycles of cisplatin; cisplatin, vincristine, and lomustine; and vincristine. The study was suspended due to 3 early failures. However, on longer follow-up, no other patient relapsed. The overall survival of this small cohort of patients was 70% + 2% at 6 years follow-up. More importantly, 6 children were tested at baseline and then again at 3 years; their mean IQ scores were 103 and 97, respectively. This study, although with a very small number of patients, suggested that standard risk medulloblastoma patients can be cured with lower doses of craniospinal irradiation and with minimal neurocognitive damage.

To address the question of necessity for entire posterior fossa boost, 32 patients with medulloblastoma (27 standard risk) were treated on another study from 1994 to 2002 with conformal tumor bed boost (54-59 Gy) and 36 Gy craniospinal irradiation in 10 patients and 23.4 Gy craniospinal irradiation in 21 patients. Adjuvant chemotherapy was given to most patients. The 5-year progression-free survival and overall survival for all patients was 84% and 85%, respectively. There were 6 relapses, and only 1 relapse was within the posterior fossa.

Based on these data, the Children’s Oncology Group is currently undertaking a clinical trial for patients between 3 and 21 years of age with standard risk medulloblastoma where children younger than 7 years of age are first randomized to receive either 23.4 Gy craniospinal irradiation or 18 Gy craniospinal irradiation and then undergo a second randomization between entire posterior fossa boost and boost to the tumor bed. Patients older than 7 years of age are nonrandomly assigned to receive 23.4 Gy craniospinal irradiation and posterior fossa boost. All patients will receive adjuvant chemotherapy. This trial is still ongoing.

Gajjar et al used craniospinal irradiation followed by high-dose chemotherapy and autologous stem-cell rescue in medulloblastoma patients between 3 and 21 years of age. Eighty-six standard risk medulloblastoma patients received 23.4 Gy craniospinal irradiation and 55.8 Gy boost to the tumor bed followed by 4 cycles of high-dose chemotherapy and autologous stem-cell rescue. The 5-year progression-free survival and overall survival was 83% and 85%, for patients with standard risk medulloblastoma, respectively. Patients with anaplastic large cell tumor had a significantly lower progression-free survival when compared to classical histology, 57% versus 77%, respectively. Another interesting finding from this study was that patients with Wingless pathway activation had a significantly better progression-free survival ($P = .03$).

**Treatment of High-Risk Medulloblastoma Patients Greater Than 3 Years of Age**

Evans et al reported on the outcome of medulloblastoma patients enrolled on Children’s Cancer Group 942 study and randomized to receive either full-dose 36 Gy...
craniospinal irradiation with a posterior fossa boost alone or similar irradiation dose but with prednisone; cisplatin, vincristine, and lomustine; and vincristine chemotherapy (prednisone; cisplatin, vincristine, and lomustine; and vincristine). For patients with high-risk medulloblastoma on this study, the 5-year progression-free survival was 48% for irradiation and chemotherapy arm versus 0% for irradiation only arm, clearly demonstrating the role of chemotherapy in this disease.\textsuperscript{47} On a successor study, Children’s Cancer Group 921, from 1986 to 1992, 203 medulloblastoma patients were randomized to receive either “eight-drugs-in-one-day” chemotherapy regimen (vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytarabine, prednisone, and cyclophosphamide) both before and after radiation therapy (36 Gy craniospinal irradiation and 54 Gy boost to the posterior fossa) or prednisone; cisplatin, vincristine, and lomustine; and vincristine chemotherapy following similar radiation dose with weekly vincristine during irradiation. Prednisone; cisplatin, vincristine, and lomustine; and vincristine chemotherapy was superior to “8-in-1” chemotherapy regimen \((P = .006).\) The 5-year progression-free survival and overall survival for patients more than 3 years of age with M0, M1, and M2 disease were 70% + 5%, 57% + 10%, and 40% + 8%, respectively. Similarly, there was a significant difference in 5-year progression-free survival estimates between nondisseminated medulloblastoma patients with greater than 1.5 cm\(^2\) residual tumor versus those with less than 1.5 cm\(^2\) residual tumor (78% + 6% and 54% + 11%, respectively).\textsuperscript{55}

Between 1992 and 2000, the International Society of Pediatric Oncology and United Kingdom Children’s Cancer Study Group treated 68 children (3 to 17 years of age) with M2 and M3 medulloblastoma with surgery followed by 4 cycles of chemotherapy followed by 36 Gy craniospinal irradiation and posterior fossa boost to 55 Gy, with similar results. The 5-year progression-free survival and overall survival for all patients were 34.7% (CI: 23.2%-46.2%) and 43.9% (CI: 32%-55.7%), respectively.\textsuperscript{56} Pediatric Oncology Group conducted a trial between 1990 and 1996 (9031) and randomized 210 high-risk medulloblastoma patients between preradiotherapy versus postradiotherapy treatment. Five-year progression-free survival and overall survival for all 210 patients enrolled on this study were 68.4% + 3.2% and 75.4% + 3%, respectively.\textsuperscript{57} Investigators from St Jude Children’s Research Hospital also used preradiation chemotherapy approach in their SJMB96 trial for 31 high-risk medulloblastoma patients, and the 5-year progression-free survival and overall survival were 70% (CI: 54%-84%) and 70% (CI: 55%-85%), respectively.\textsuperscript{41} Children’s Oncology Group then undertook a study for high-risk medulloblastoma patients between 3 and 18 years of age to determine the feasibility of administering daily carboplatin during irradiation as a radiosensitizer, followed by maintenance chemotherapy. All patients received full-dose craniospinal irradiation to 36 Gy followed by entire posterior fossa boost. Four-year progression-free survival and overall survival for the entire group of 57 enrolled patients were 66% + 6% and 81% + 5%, respectively. Presence of severe anaplasia was once again a significant negative predictive factor with a 4-year progression-free survival of 48% + 12% and 76% + 7% for patients with and without anaplasia, respectively \((P = .02).\) In the currently open Children’s Oncology Group study, patients with high-risk medulloblastoma are being randomized upfront between irradiation with or without daily carboplatin followed by maintenance chemotherapy. The impact of isotretinoin as a differentiating agent is also being investigated in this study. This study is currently ongoing.

**Treatment of Infants and Young Children (Greater Than 3 Years of Age) With Medulloblastoma**

Treatment of medulloblastoma in infants is particularly challenging. The survival of infants with medulloblastoma is inferior to that in older children as the tumors are typically large at presentation, tumors are more vascular, and there is a high incidence of leptomeningeal spread and there is a lower chance of achieving a gross total resection. Needless to say, the sequelae of radiation therapy on the developing brain of young children often outweighs the benefits of irradiation specifically with regard to learning difficulties, attention/concentration difficulties, short-term memory deficits, social adjustment problems, hearing, speech and language problems, and impaired physical growth from radiation to the pituitary, hypothalamus, and the vertebral bodies. Hence, there is the need for irradiation-avoiding strategies in this age group of patients with medulloblastoma.

The survival of infants with malignant brain tumors was extremely poor prior to the use of adjuvant chemotherapy. In a report from United Kingdom Children’s Cancer Study Group on treatment of 548 young children younger than 3 years of age from 1971 to 1985, the overall survival for patients with ependymoma was 20% and medulloblastoma was 13%.\textsuperscript{59} In the United States, Surveillance Epidemiology and End Results data from 1961 until 1979 reported survival rates of ependymoma patients to be 12% and medulloblastoma patients at 18%.\textsuperscript{60} Van Eys et al\textsuperscript{61} first documented the effectiveness of chemotherapy in infants with medulloblastoma. Of 17 infants with malignant brain tumors (6 with medulloblastomas) treated with nitrogen mustard, vincristine, procarbazine, and prednisone from 1976 to 1988, 15 responded to this regimen and 6 of 15 responders were long-term survivors. In a follow-up report of this study published by Ater et al,\textsuperscript{62} 8 of 12 patients with medulloblastoma were long-term survivors at 6 to 16 years of follow-up. This
report suggested that long-term survival was possible in medulloblastoma patients without irradiation.

In the 1980s, Pediatric Oncology Group conducted the first landmark study for the treatment of infants and young children with malignant brain tumors using postoperative chemotherapy for an extended period of time in an attempt to delay radiation therapy (Baby Pediatric Oncology Group 1). Patients younger than 24 months of age received chemotherapy for 24 months and those between 24 and 36 months of age received chemotherapy for 12 months. At the end of chemotherapy, patients with no evidence of disease received craniospinal irradiation to 24 Gy with a boost to 50 Gy to the primary site and patients with residual disease received 36 Gy craniospinal irradiation and a boost to 54 Gy. For 62 medulloblastoma patients, the 5-year progression-free survival and overall survival were 31.8% + 3% and 39.7% + 6.9%, respectively. The survival for children with complete resection of the tumor was 69% at 5 years. Another interesting finding from this study was that most relapses occurred within the first 6 months and no relapses after 2 years.63,64 Similar progression-free survival data in the range of 45% to 50% were also reported by other international cooperative groups, using irradiation delaying/avoiding strategies.65-67 Children’s Cancer Group conducted a trial (Children’s Cancer Group 921) where 46 children younger than 18 months of age received the “8-in-1” chemotherapy regimen following surgery. Radiation therapy was recommended on this protocol for all these children; however, most of the patients did not receive radiotherapy. The 3-year progression-free survival for all medulloblastoma patients was 22% + 6%.68 The survival for patients with gross total resection and no metastatic disease was 30% at a median follow-up time of 72 months on this study compared to 69% on the Baby Pediatric Oncology Group 1 study. Once again on this study, it was observed that most patients progressed within the first 6 months, suggesting that withholding irradiation for 1 to 2 years may not alter the progression-free survival.

In a successor study by Children’s Cancer Group (Children’s Cancer Group 9921), 299 children less than 36 months of age with malignant brain tumors (92 children with medulloblastoma) were randomly assigned to 1 of the 2 induction chemotherapy regimens following surgery (vincristine, cisplatin, cyclophosphamide, and etoposide vs vincristine, carboplatin, ifosfamide, and etoposide). Patients with disseminated disease at diagnosis or with persistent residual disease after induction chemotherapy received irradiation when they reached 3 years of age or on completion of maintenance phase (whichever came first) or on relapse/progression. The 5-year progression-free survival and overall survival rates for standard risk medulloblastoma patients were 41% + 8% and 54% + 8%, respectively, and 5-year progression-free survival and overall survival rates for disseminated medulloblastoma patients were 25% + 8% and 31% + 9%, respectively. For patients with medulloblastoma, 83% of 5-year progression-free survivors had never received irradiation. There was no significant difference in outcomes between both arms of the study,69 and the intensified chemotherapy in this study did not provide a significant survival advantage when compared to Children’s Cancer Group 921. Pediatric Oncology Group also conducted a randomized study where standard chemotherapy was compared with dose-intensive chemotherapy (9233). Preliminary data suggested no significant benefit for dose intensification.70

Grill et al71 reported the results of the French Society of Pediatric Oncology trial conducted in the early 1990s using postoperative chemotherapy without any radiotherapy. Patients were to receive conventional dose chemotherapy with carboplatin, procarbazine, etoposide, cisplatin, vincristine, and cyclophosphamide. Patients who progressed received salvage treatment with high-dose chemotherapy and stem-cell transplantation followed by local or craniospinal irradiation. Patients who did not relapse did not receive irradiation. The 5-year progression-free survival and overall survival rates for standard risk medulloblastoma patients were 29% (CI: 18%-44%) and 73% (CI: 59%-84%), respectively, and 5-year progression-free survival and overall survival rates for disseminated medulloblastoma patients were 13% and 13%, respectively.71 This study showed that it was possible to cure a significant number of young children with localized disease and gross total resection without craniospinal irradiation.

The German national cooperative group has published encouraging data for children with standard risk medulloblastoma, using a conventional chemotherapy regimen to which was added both systemic and intraventricular methotrexate, and which avoided the use of irradiation. The 5-year progression-free survival and overall survival rates for patients with complete resection of localized disease were 82% + 9% and 93% + 6%, respectively, and the 5-year progression-free survival and overall survival for patients with disseminated disease were 33% + 14% and 38% + 15%, respectively.12 Almost 50% of the patients on this study had desmoplastic medulloblastoma, which could account for the improved progression-free survival / overall survival. Although these data represent the best EFS and overall survival yet published for young children (less than 3 years of age) with newly diagnosed, standard risk medulloblastoma, there is significant concern that the methotrexate contributed to impairments in cognitive and developmental functioning.

Recognizing the early median time to progression of young children with medulloblastoma on the Baby Pediatric Oncology Group 1 and early Children’s Cancer Group studies, the “Head Start” studies were initiated in 1991. Induction chemotherapy consisted of 5 cycles of cisplatin, vincristine, etoposide, and cyclophosphamide on Head Start I study. Patients with disseminated medulloblastoma received high-dose methotrexate in addition
to other chemotherapeutic agents in each cycle, on Head Start II. After induction chemotherapy, patients would proceed directly to consolidation phase with myeloablative chemotherapy and autologous stem-cell transplant. The 5-year progression-free survival and overall survival rates for patients with complete resection of localized disease were 64% + 13% and 79% + 11%, respectively, and the 5-year progression-free survival and overall survival for disseminated medulloblastoma patients were 45% (95% CI: 24%-64%) and 54% (95% CI: 31%-72%), respectively. Similar to the French study, 50% of survivors with standard risk medulloblastoma did not receive radiation therapy. More interestingly, 6 of 12 survivors with disseminated medulloblastoma who are alive with no evidence of disease 5 years from diagnosis have not received radiation therapy. The results of the various infant protocols are summarized in Table 1.

Children’s Cancer Group has completed a pilot study (Children’s Cancer Group 99703) to evaluate the feasibility of the administration of 3 cycles of chemotherapy with cisplatin, cyclophosphamide, etoposide, and vincristine followed by 3 sequential cycles of high-dose chemotherapy using thiotepa and carboplatin with autologous peripheral blood stem-cell rescue in infants with malignant brain tumors. The final results of this trial have not yet been reported. In the currently open Children’s Oncology Group trial (0334), patients less than 36 months of age with high-risk medulloblastoma are being randomized to receive 3 cycles of chemotherapy (similar to Children’s Cancer Group 99703, as described above) with and without high-dose methotrexate followed by 3 sequential cycles of high-dose chemotherapy using thiotepa and carboplatin with autologous peripheral blood stem-cell rescue. This study is ongoing.

**Table 1. Five-Year Progression-Free Survival and Overall Survival on Various Infant Protocols**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>R1M0 Patients 5-Year PFS (%) + SD</th>
<th>R1M0 Patients 5-Year OS (%) + SD</th>
<th>R0M0 Patients 5-Year PFS (%) + SD</th>
<th>R0M0 Patients 5-Year OS (%) + SD</th>
<th>M + Patients 5-Year PFS (%) + SD</th>
<th>M + Patients 5-Year OS (%) + SD</th>
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<tbody>
<tr>
<td>Baby POG-163,64</td>
<td>31.8 + 8.3</td>
<td>39.7 + 6.9</td>
<td>No data</td>
<td>69</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>BR-SFOP11</td>
<td>6 (CI: 1-27)</td>
<td>41 (CI: 22-64)</td>
<td>29 (CI: 18-44)</td>
<td>73 (CI: 59-84)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Children’s Cancer Group 92168</td>
<td>22 + 6 (3y PFS)</td>
<td>No data</td>
<td>No data</td>
<td>30</td>
<td>11 + 6</td>
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</tr>
<tr>
<td>Children’s Cancer Group 992169</td>
<td>26 + 9</td>
<td>40 + 11</td>
<td>41 + 8</td>
<td>54 + 8</td>
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<td>31 + 9</td>
</tr>
<tr>
<td>HIT-SKK’9212</td>
<td>58 + 9</td>
<td>66 + 7</td>
<td>82 + 9</td>
<td>93 + 6</td>
<td>33 + 14</td>
<td>38 + 15</td>
</tr>
<tr>
<td>“Head Start” I and II72-74</td>
<td>29 + 17</td>
<td>57 + 19</td>
<td>64 + 13</td>
<td>79 + 11</td>
<td>45</td>
<td>54</td>
</tr>
</tbody>
</table>

CCG, Children’s Cancer Group; HIT-SKK, German Pediatric Brain Tumor Study Group trial; M0, nondisseminated disease; M1, disseminated disease; OS, overall survival; MB, medulloblastoma; POG, Pediatric Oncology Group; PFS, progression-free survival; R1, less than gross total resection; R0, gross total resection; SFOP, French Society of Pediatric Oncology.

**Future Directions**

Although significant progress has been made recently in understanding the molecular pathogenesis, diagnosis, and treatment of medulloblastoma, much remains to be achieved. We still need to understand the cellular origin of medulloblastoma cells, understand pathogenesis and dissect the critical pathways responsible for these tumors, and formulate risk stratification schemas based on
molecular markers in addition to clinical factors. Once we identify molecular targets and pathways that are important in medulloblastoma, we need to develop targeted therapy that will inhibit these processes in the cancer cells and hence spare other organs from long-term toxicities of irradiation and chemotherapy. Development of animal models of medulloblastoma that truly mimic disease in humans will be very important in understanding the pathogenesis and development of new therapies in the future. Although a significant proportion of infants and children with standard risk medulloblastoma are curable, better treatments are needed for patients with high-risk disease. Because irradiation is an integral part of medulloblastoma therapy, we still need to study the long-term sequelae of radiation therapy in the era of intensity-modulated radiation therapy and proton beam irradiation and continue to strive to devise better treatments, especially for infants and young children with medulloblastoma.

References


