Cancer, Medulloblastoma

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Introduction

While leukemias are the most common type of malignancy to afflict the pediatric population, brain tumors are the most common solid tumors in this age group. Medulloblastoma is the most common malignant brain tumor in children, accounting for 20% of all pediatric brain tumors. It is categorized as a primitive neuroectodermal tumor of the cerebellum. While mortality within the first two years of diagnosis can be approximately 10% to 15%, cure rates can reach as high as 60% with current therapeutic modalities. Surgical resection, preceded and/or followed by radiation and chemotherapy, is the mainstay of therapy, with five-year survival rates of between 50% to 90%; this wide range is multifactorial, owing in part to age at diagnosis, the presence of metastases at diagnosis, and a histologic variant of Medulloblastoma. Regardless of long-term survival, treatment-related neurologic, cognitive, and endocrinologic sequelae remain a debilitating concern and an impetus for the search for novel therapeutics.

Etiology

While no clear etiology has been identified, a link may exist with maternal diet and blood or immune disorders during pregnancy, early JC viral infections in childhood, or human cytomegalovirus.

Epidemiology

With a ten-fold higher incidence in pediatrics than adulthood, data from the Surveillance, Epidemiology, and End-Results database reported an estimated annual incidence for medulloblastoma in the United States of six per million children or approximately 450 new pediatric cases per year. The peak age of onset is between four and nine years of age. Younger age at diagnosis portends poorer prognosis due to the more aggressive nature of the tumor at diagnosis. It is seen more frequently in boys than girls (1.5:1).

Pathophysiology
Thought to originate from the granule cell precursors in the external germinal layer of the developing cerebellum, tumor growth starts along the floor of the fourth ventricle and occupies the entirety of the ventricle, subsequently invading both the cerebellar vermis and the brainstem. Medulloblastoma is a highly malignant tumor with a propensity for local invasion and distant metastatic spread through the subarachnoid system, in other words, within the brain and along the spinal cord, also known as "drop mets." Extraneural metastases are an infrequent occurrence (approximately 7%). The most frequent sites of extraneural metastasis in children include bone (78%), lymph nodes (33%), liver (15%), and lungs (11%) with the average time to development after maximal surgical resection being approximately 20 months. Survival in these cases is dismal, and in most cases, can be less than six months.

The most common cytogenetic abnormality in medulloblastoma is i17q, (isochromosome 17q), wherein the short arm (p) is absent, and there is a gain of genetic material from the long arm (q). In more than 50% of patients, deletions in the short arm have been reported, resulting in a genotypic designation as 17pLOH, in other words, the loss of heterozygosity of 17p. Of note, the tumor suppressor gene, TP53, is located on chromosome 17p. However, mutations in TP53 are a low-frequency occurrence in medulloblastoma. Thus, the search for putative tumor suppressor genes on chromosome 17p in the context of medulloblastoma is ongoing.

**History and Physical**

Symptomatology often reflects the course of tumor spread. Patients may present with gait disturbances and/or clumsiness, namely cerebellar signs. They may concurrently complain of early morning headaches, nausea, and vomiting due to obstructive hydrocephalus. Other common symptoms include visual disturbances, like double vision or blurry vision. Time from symptom onset to diagnosis is usually about two to three months.

**Evaluation**

Patients with medulloblastoma were traditionally risk stratified into average-risk or high-risk groups based on (1) age at diagnosis, (2) extent of postoperative residual disease, and (3) degree of tumor metastasis at diagnosis. Although cure rates in the average-risk group reached three-quarters of patients, post-surgical treatment-related neurologic, cognitive, and endocrinologic sequelae remained a source of morbidity in up to 80% of survivors. The high-risk group experienced up to 50% mortality due not only to the presence of extraneural metastases at diagnosis but also due to a young age at diagnosis, which posed significant limitations to therapeutic options, namely lower doses of radiation and chemotherapeutic agents.

Traditional risk stratification discounted the prognostic importance of tumor histology. Moreover, recent transcriptional profiling studies of large numbers of patients with medulloblastoma revealed clusters of patients with cytogenetic signatures and gene expression distinct to unique signal transduction pathways. With a marriage of these molecular and histologic signatures emerged the current classification system that divides patients into four primary subgroups: (1) SHH, sonic hedgehog; (2) WNT, wingless; and (3) non-SHH/WNT groups 3 and 4.

Histologically, the World Health Organization divides medulloblastoma into five basic types based on genetic profile and histology: (1) WNT-activated
with classic histology; (2) SHH-activated (wild-type TP53), with classic, desmoplastic/nodular, or large-cell/anaplastic histology; (3) SHH-activated (mutant TP53), with classic or large-cell/anaplastic histology; (4) non-WNT/non-SHH, group 3, with classic or large-cell anaplastic histology; and (5) non-WNT/non-SHH, group 4, with classic or large-cell/anaplastic histology.

Classic histology is defined by sheets of small round blue cells with high nuclear-to-cytoplasmic ratio and neuroblastic differentiation. Desmoplastic nodular histology demonstrates nodules of tumor cells with neurocytic differentiation on a collagen-rich matrix. Large-cell anaplastic histology is characterized by large cells with abundant cytoplasm and prominent nucleoli; they have a high mitotic index and are aggressive.

**Treatment / Management**

The mainstay of treatment for medulloblastoma is maximal surgical resection followed by chemotherapy and whole neuraxis radiation. However, average-risk patients suffer from post-treatment morbidity, including intellectual retardation and growth hormone deficiency, while high-risk patients suffer a dismal five-year disease-free survival due to limitations on therapeutic options due to young age.

Newer subgroup classification systems have facilitated the development of more targeted therapeutics aimed at disrupting signal transduction pathways critical to phenotypic transformation. These are currently under clinical investigation.

**Wingless (WNT) Subgroup Tumors**

The key step in WNT signal transduction leading to malignant transformation is a lack of degradation of $\beta$-catenin due to mutations at key amino acid residues that are normally destined for phosphorylation. Hence, new drugs have been developed to target steps in downstream signaling by $\beta$-catenin. These include naturally-occurring protein phosphatase inhibitors, cantharidin, norcantharidin, and ginkgetin.

**SHH Subgroup**

The SHH pathway is activated by the binding of Sonic Hedgehog to its receptor Patched 1 (PTCH1) which activates downstream signaling via a key mediator Smoothened (SMO). The most widely studied targeted therapeutic agents today are SMO inhibitors such as cyclopamine, HhAntag, vismodegib, saridegib, and sonidegib. In fact, sonidegib is currently in phase II/III trials in both adult and pediatric patients.

**Non-SHH/WNT Subgroup**

Unfortunately, not much is known about the signaling pathways implicated in non-SHH/WNT subgroup medulloblastoma. As a result, targeted therapeutics have yet to be developed for this type of medulloblastoma.

**Questions**
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References


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