

ADVANCES IN PEDIATRIC HEM/ONC

Current Developments in the Management of Childhood Malignancies

Section Editor: Mitchell S. Cairo, MD

Advances in the Diagnosis and Treatment of Malignant Childhood Brain Tumors

Sridharan Gururangan, MRCP (UK)
Director of Pediatric Clinical Services
Associate Professor of Pediatrics and Surgery
Preston Robert Tisch Brain Tumor Center
Duke University Medical Center
Durham, NC

H&O What is the annual incidence of pediatric brain tumors?

SG Pediatric brain tumors are the second most common tumor type in children. Approximately 2,200 such patients are diagnosed each year in the United States, an estimated 7–8 children on an average weekday. The outcomes for these patients have improved over the past 20 years but have not kept pace with the improvements seen in other malignant diseases, such as pediatric leukemias. In fact, the proportion of cancer deaths in children due to brain tumors has increased from 18% to 30% over the past two decades.

H&O How does this malignancy in children compare with that occurring in adults?

SG In adults, the incidence of brain tumors is approximately 10-fold higher than in children. The predominant diagnosis in adults is malignant glioma, whereas children mostly have low-grade tumors, including pilocytic astrocytoma, desmoplastic neuroepithelial tumor, ganglioglioma, or central neurocytoma. The most common malignant brain tumor in children is medulloblastoma, an embryonal tumor that originates in the superior medullary velum of the cerebellum. Other malignant brain tumors in children include pineoblastoma, cerebral primitive neuroectodermal tumor (PNET), ependymoma, atypical teratoid rhabdoid tumor, and germ cell tumors.

In general, children with brain tumors are more easily curable than adults. This is partly due to the higher proportion of patients (>90%) with low-grade tumors who can be cured with surgical resection alone. In addition, older children (>3 years of age) with localized medulloblastoma have a 5-year progression-free survival of over 75% when treated with irradiation (craniospinal plus focal boost) and systemic chemotherapy. For adults with glioblastoma multiforme, the survival rate is less than 10% at 1 year following diagnosis. Overall, about two thirds of children with brain tumors can be cured of their disease using a combination of surgery, chemotherapy, and radiotherapy (focal with or without craniospinal irradiation).

H&O What are the particular considerations with regard to the treatment of pediatric patients?

SG Unlike adults, who can receive all treatment modalities relatively safely, young children with brain tumors are particularly susceptible to the side effects of chemotherapy and radiation therapy on the developing brain, resulting in growth failure and neurocognitive deficits. Therefore, it is necessary to create treatment strategies that avoid some of the side effects especially associated with craniospinal irradiation. Ongoing research is aimed at delaying, limiting, or avoiding radiotherapy to the neuraxis but still providing dose-intensive chemotherapy to eradicate the tumor.

H&O How are childhood brain tumors diagnosed?

SG The most useful diagnostic method for brain tumors in both children and adults is magnetic resonance imaging (MRI) of the brain as it provides exquisite anatomic detail. Computed tomography (CT) scans may be used in urgent situations, when a patient presents in the emergency room with symptoms of raised intracranial pressure possibly due to a space-occupying lesion. In this situation, a CT scan of the brain with or without contrast would adequately demonstrate the presence or absence of hydrocephalus and/or a space-occupying lesion. An MRI scan of the brain can subsequently be done to obtain a better idea of the location and extent of this lesion. The neurosurgeon then obtains a biopsy of the mass in order to get a definitive diagnosis of

a brain tumor. Using special stains, immunohistochemistry, and molecular methods, the neuropathologist is able to obtain a specific histologic diagnosis and subclassify the tumor in order to assess prognosis.

H&O Is it always possible to obtain a biopsy with a pediatric patient?

SG The decision to perform a biopsy depends on the anatomical location of the tumor. Whereas adult tumors typically occur in the cerebral hemispheres, childhood tumors are typically located in the infratentorial compartment, in particular the cerebellum and IV ventricle, or in more midline structures including the optic pathway, hypothalamus, thalamus, or brain stem. It is particularly unsafe to biopsy lesions within the brain stem or optic pathways. Attempts at biopsy of such tumors could result in injury to the brain stem and cause problems with swallowing, motor function, and cranial nerve palsies. Biopsy of tumors in the optic pathways can worsen existing visual impairment. The expertise of the pediatric neurosurgeon plays a key part in the functional outcome following surgery. The operating microscope and ultrasonic surgical aspirator allows the surgeon to perform an adequate tumor resection without compromising the adjacent normal brain. Preoperative imaging can be correlated with intraoperative observation using a frame-based or frameless system that also help in guiding the surgeon with trajectories to deep-seated lesions. Functional MRI, positron emission tomography (PET), and electrode grids for mapping areas of the cerebral cortex have helped the surgeon to accurately delineate tumor margins and improve surgical morbidity in these patients. Most studies of both low- and high-grade pediatric brain tumors have demonstrated that complete resection results in improved prognosis.

H&O What other methods are being explored for diagnosing pediatric brain tumors?

SG In addition to proper anatomical localization using conventional neuroimaging including a CT or MRI scan of the brain, there is an increasing interest in establishing the functional characteristics of brain tumors. Magnetic resonance spectroscopy is a fairly well established method that can differentiate between normal and neoplastic tissue on the basis of differing chemical composition. Whereas normal brain demonstrates an elevated peak of N-acetyl aspartate (NAA, a neurotransmitter present in normal neurons) and a smaller peak of choline (reflecting minimal cell turnover in normal brain), tumor tissue exhibits an elevated choline peak (due to increased cell membrane turnover) and a diminished NAA peak (due to a paucity

of normal brain tissue within the tumor). Dynamic contrast-enhanced imaging measures the blood flow and permeability within tumors as compared to normal brain and can be used to determine prognosis and changes within a tumor resulting from certain new therapies that target tumor angiogenesis. Similarly, diffusion weighted imaging, which measures movement of water within tumor or normal tissue, can be utilized in assessing changes in tumor cellularity with treatment. Fluorodeoxyglucose (FDG) PET can be useful for diagnosing brain tumors. This approach, which involves injecting radioactive glucose and imaging the brain using a gamma camera, relies on the ability of the tumor to take up glucose and retain it for a longer time than the normal brain. The degree of malignancy is then dependent on the degree of glucose uptake. Several studies have explored the utility of FDG-PET scans in the diagnosis of brain tumors and assessing prognosis based on the tumor FDG uptake. Newer isotopes that have better tumor selectivity, including F-18 fluorodeoxycholine and C-14 methionine, are currently being tested in patients with brain tumors.

H&O What advances are being made in the treatment of childhood brain tumors?

SG In recent years, it has become apparent that treatment failures are usually due to the presence of an intact blood-tumor barrier and drug resistance. Current strategies are aimed at circumventing this barrier and overcoming resistance to chemotherapy. In addition, there has been an explosion in the research of biologic therapies.

The National Cancer Institute created (in 1999) and funds the Pediatric Brain Tumor Consortium (PBTC), which now has 10 participating institutions in the United States. The PBTC is charged with rapidly developing new treatments for pediatric brain tumors. The group has successfully completed several trials of novel therapies for the treatment of pediatric brain tumors.

The treatment of pediatric brain tumors has been traditionally focused on chemotherapeutic agents that can cross the blood-brain barrier, such as alkylating agents including cyclophosphamide, nitrosoureas, cisplatin, and carboplatin. In the last 5 years, temozolomide, an oral methylating agent, has been increasingly used for this disease. Because fat-soluble alkylating agents readily cross the blood-tumor barrier, treatment failure is typically due to drug resistance. The most characterized mechanism of drug resistance is due to overexpression of a DNA repair enzyme called alkyl guanine alkyltransferase (AGT). It is likely that depletion of this enzyme will improve cell kill from alkylating agents whose predominant mode drug resistance is AGT overexpression. O-6 benzyl guanine (O-6BG) is a specific drug that has been used to deplete

tumor cells of AGT prior to administration of alkylating agents including carmustine (BCNU) and temozolomide. The PBTC has completed a phase I trial of temozolomide plus O-6BG in children with recurrent brain tumors. A PBTC phase II trial of this combination is currently accruing patients with recurrent high-grade supratentorial and diffuse brain stem gliomas.

Treatments aimed at circumventing the blood-tumor barrier include intrathecal therapy, intracavitary therapy, and convection enhanced delivery (CED). Intrathecal chemotherapy uses chemotherapeutic agents like mafosfamide, thiotepa, busulfan, or topotecan directly into the spinal fluid to treat brain tumors that have spread along the leptomeninges. The PBTC has completed one phase I trial involving a novel formulation of busulfan (Spartaject Busulfan, SuperGen) in children with recurrent brain tumors and leptomeningeal disease (LMD). An ongoing PBTC phase I trial is exploring topotecan intrathecally using a prolonged schedule in children with LMD. Intracavitary chemotherapy using Gliadel Wafers (MGI Pharma) that are placed into the cavity of the tumor during surgical resection delivers a high concentration of BCNU into the margins of the tumor. This therapy is applicable only for tumors like malignant gliomas that progress by local infiltration rather than metastatic spread. Randomized phase III trials in adults with recurrent malignant glioma have demonstrated a marginal survival advantage (8–10 weeks) in patients who receive Gliadel Wafers plus radiotherapy as compared to radiotherapy alone.

Convection-enhanced delivery is a recently described method of delivering large molecules via a micro-infusion pump directly into the tumor using strategically placed catheters. Both phase I adult and pediatric trials are underway using fusion proteins made up of pseudomonas exotoxin and either transforming growth factor or interleukin-13. The latter molecules are designed to target the glioma cells and spare normal brain tissue. Once the glioma cells are targeted, the exotoxin is internalized and causes cytotoxicity.

H&O What are some of the targets for biologic agents in pediatric brain tumors?

SG The most common molecular alterations in high-grade gliomas include p53 mutations, epidermal growth factor receptor (EGFR) amplification, loss of heterozygosity on chromosome 10 (involving the phosphatase and tensin homology gene) and 19, and platelet-derived growth factor (PDGFR) α gene amplification. There has been a profusion of studies describing the molecular characteristics of medulloblastoma including the Sonic-Hedgehog and WNT signaling pathways, Trk-C expression, c-Myc amplification, presence of isochromosome 17q, ERBB-3

and -4 overexpression, and PDGFR α and RAS/MAP-kinase activation that can predict the biologic behavior and outcome independent of clinical characteristics.

Brain tumors beyond a certain size (usually 1 mm³) depend on an influx of new blood vessels that initiate an exponential increase in tumor size, infiltration, and metastasis by a process called tumor angiogenesis. This is mediated by several proangiogenic factors including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF).

H&O What approaches are being explored that make use of these potential therapeutic targets?

Some of these molecular markers of disease have been chosen as targets for inhibition using small molecule protein kinase inhibitors including ZD1839 (Iressa, AstraZeneca) and lapatinib (GlaxoSmithKline) targeting EGFR and imatinib mesylate (Gleevec, Novartis) targeting the PDGFR. These small molecule inhibitors might have some indirect negative effect on tumor angiogenesis. Phase I/II trials of these drugs are ongoing in children with newly diagnosed and recurrent high-grade gliomas (including diffuse pontine glioma), medulloblastoma, and ependymoma through the PBTC. Future studies will address whether such small molecule protein kinase inhibitors work additively or synergistically with chemotherapeutic or antiangiogenic agents. The efficacy of 13 cis-retinoic acid will be tested in an upcoming phase III trial in children with newly diagnosed high-risk PNETs as a backbone to standard chemotherapy and irradiation.

The PBTC is also conducting some key antiangiogenesis trials in children with recurrent brain tumors. These include the combination of bevacizumab (Avastin, Genentech) and irinotecan (Camptosar, Pfizer) in children with recurrent malignant glioma and diffuse brain stem gliomas, phase I studies of lenalidomide (Revlimid, Celgene) and AZD 2171 (a VEGF-R2 inhibitor) in children with recurrent brain tumors.

Suggested Reading

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