Brain Tumors in Children

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Childhood brain tumors are the leading cause of cancer-related morbidity and mortality in the pediatric years and differ from primary central nervous system tumors occurring in adults. Management strategies must take into account not only the tumor type, but the age of the patient and the likelihood of treatment-induced nervous system damage. With current means of treatment, most children older than 3 years can be effectively treated. Chemotherapy has taken on an increasing role in the treatment of childhood medulloblastomas, low-grade gliomas, and high-grade gliomas. Some tumor types, especially atypical teratoid tumors, brainstem gliomas, malignant gliomas, and malignant infantile tumors, remain significant therapeutic dilemmas.

Childhood brain tumors differ from those arising in adulthood in their relative incidences, histological features, sites of origin, and responsiveness to therapy. Most childhood brain tumors are primary central nervous system lesions occurring in 2.5 to 4 per 100,000 children at risk per year. Tumors of the nervous system are now the most common form of childhood malignancy and the leading cause of cancer-related morbidity and mortality. The reported incidence of primary central nervous system tumors in children has increased by 35% over the past 2 decades, and this apparent increase has raised serious concern that environmental exposures are causative. Despite multiple recent epidemiological studies, including those investigating parental occupational exposures, other environmental exposures, and maternal nutritional intake, including the use of prenatal vitamin supplementation, direct links between such factors and the development of childhood brain tumors have not been proven. In addition, the reported increased incidence has been suggested by some to be an artifact of better diagnosis owing to the availability of magnetic resonance imaging scanning beginning in the 1980s.

The management of childhood brain tumors is far from optimal and continues to evolve. Treatment decisions are not only based on the type of tumor and its location in the central nervous system, but also on the age of the child and the effects therapy may have on the developing nervous system. Complicating factors further is the relative infrequency of any specific subtype of childhood brain tumor; prospective randomized studies are difficult, if not impossible, to complete in all but a few types of primary central nervous system malignancies. Also retarding progress in management of childhood brain tumors is the lack of understanding of the basic biological characteristics of many of these tumors, especially embryonal tumors. Knowledge in this area lags behind biologic advancements in other childhood tumors, such as leukemias and neuroblastomas, and, for that matter, even adult malignant gliomas. Despite these substantial obstacles, progress is being made in the care of childhood brain tumors, and management strategies have changed considerably over the past decade.

CHILDHOOD EMBRYONAL TUMORS

Medulloblastomas and Other Primitive Neuroectodermal Tumors

Primitive neuroectodermal tumors, including medulloblastomas, are the single most common form of childhood brain tumor. Although these tumors arise predominantly in the posterior fossa, histori-
Since the mid 1980s, it has been accepted that childhood primitive neuroectodermal tumors can be broadly separated into 2 risk groups. A more favorable, or “average,” risk group includes those children with posterior fossa tumors and those whose tumors are localized at the time of diagnosis. Children with nonposterior fossa tumors and/or those with disseminated lesions at the time of diagnosis have a less favorable prognosis. Extent of surgical resection at the time of initial surgery has been shown by most studies to be of importance in patients with localized disease at the time of diagnosis, as those patients with total or near-total resections fare better than those whose tumors are subtotally resected. In every prospective study to date, age has been predictive of outcome, as younger children seem to fare less well. However, the reasons for the relationship between age and outcome remain unclear.

The biological underpinnings of primitive neuroectodermal tumors are poorly understood. Although some studies have indicated a relationship between cytogenetic findings (the presence of an isochromosome 17q) and DNA ploidy results and outcome, no specific biological marker has been reproducibly found to be associated with prognosis or with the likelihood of tumor dissemination. Recently, studies have focused on mutations or abnormal expressions in neural developmental genes, neurotrophin and neurotrophin receptors (high expression of tyrosine kinase receptors being associated with a more favorable outcome), and amplification of C-MYC (associated with a poorer outcome). Larger prospective studies are needed to determine if these new biological factors will supplement, or supplant, the significance of clinical factors.

Despite the lack of basic understanding of medulloblastomas and other primitive neuroectodermal tumors, clinical progress has been made. Treatment with craniospinal (36 Gy) and local boost radiotherapy (total dose 54 Gy) results in long-term disease control in approximately 60% of children with posterior fossa tumors. Disease control for patients with pineoblastomas and cortical primitive neuroectodermal tumors is worse than for those with posterior fossa lesions, and it is not known why. Prospective randomized trials have demonstrated that the addition of chemotherapy, during and after radiation therapy, using the combination vincristine sulfate and lomustine (CCNU) regimen improves outcome for those patients with more extensive disease at the time of diagnosis. Such randomized trials have never clearly proven that patients with average-risk disease benefit from the addition of chemotherapy; however, pilot studies have suggested as good, if not better, outcome in patients with poor-risk disease treated with radiation and chemotherapy compared with those with average-risk disease treated with radiation alone. In the largest single-arm study performed to date, 63 patients with incompletely resected or disseminated medulloblastomas treated with craniospinal radiation followed by 8 cycles of CCNU, vincristine, and cisplatin chemotherapy had a 5-year, progression-free survival rate of 85% ± 6% SD. In this trial, patients with localized disease at the time of diagnosis had a 5-year, progression-free survival rate of over 90%, while those with disseminated disease had a 67% ± 15% survival rate. Attempts at improving this survival rate even further, especially for those children with metastatic disease at the time of diagnosis and those with nonposterior fossa tumors, are underway. One approach has been to use preirradiation chemotherapy, and although responses can be seen in some patients, preirradiation chemotherapy trials to date have not demonstrated an improved rate of survival. In one completed randomized study, children received the 8-drug-in-1-day approach prior to and after radiation therapy, or CCNU and vincristine during and after radiation therapy. Children receiving the preirradiation chemotherapy arm of the study did not fare as well as those receiving adjuvant drug therapy during and after radiation therapy. Other approaches underway include the use of more aggressive chemotherapy during irradiation and the use of high-dose chemotherapy, following radiation therapy, supported by autologous bone marrow transplantation or peripheral stem cell support.

In treating children with nondisseminated medulloblastomas, attempts have been made to reduce the dose of craniospinal radiation therapy owing to concerns of long-term toxic effects of radiotherapy on the developing nervous system. After 36 Gy of craniospinal radiation therapy, many children will have significant long-term neurocognitive sequelae, including demonstrable drops in overall intelligence. One study was performed comparing 23.4 Gy of craniospinal irradiation with the conventional 36 Gy of craniospinal irradiation in children with nondisseminated medulloblastomas. All children received the same total dose of local radiotherapy, and no adjuvant chemotherapy was given. This study was closed prior to full accrual of patients, as interim analysis disclosed a poorer disease-free survival rate and higher rate of isolated neuroaxis relapses in patients who received the reduced-dose craniospinal radiation therapy. However, further follow-up of patients entered in this study has shown a questionable (borderline statistically significant) difference in overall survival rates between patients in the 2 treatment arms. A more recent prospective cooperative group study did not demonstrate a difference in overall survival rate between those patients receiving reduced-dose craniospinal radiation therapy compared with those receiving conventional doses of craniospinal radiation therapy, as long as preradiation therapy was not used. A nationwide prospective single-arm pi-
lot study was recently completed using reduced-dose craniospinal radiation therapy (23.4 Gy), standard local radiotherapy and adjuvant CCNU, vincristine, and cisplatin chemotherapy being given during and after radiation therapy. After 3 years, the progression-free survival for 68 children aged 3 to 10 years with nondisseminated medulloblastomas treated with this approach was 86% ± 4% SD. Neurocognitive studies have demonstrated that reducing the dose of craniospinal radiation therapy will result in fewer long-term intellectual sequelae. A prospective study is presently underway using reduced-dose craniospinal radiation therapy in all children with nondisseminated medulloblastomas comparing 2 different chemotherapy treatment arms that use chemotherapy during and after radiation therapy.

An extremely difficult-to-treat subset of patients with medulloblastomas or other primitive neuroectodermal tumors are infants or very young children. Studies have demonstrated a poorer overall survival rate, a higher likelihood of early tumor dissemination, and more frequent severe neurocognitive sequelae after standard treatment in younger patients. A subset of patients younger than 3 years can be successfully treated with chemotherapy alone. A variety of different chemotherapeutic approaches has been used, and no one approach seems to be superior. At the present time, work is focusing on high-dose chemotherapy supplemented with peripheral stem cell support to obtain a higher rate of initial disease control. However, since many children will experience a relapse after initial disease control, even while receiving maintenance chemotherapy, there is renewed interest in the use of some form of radiation therapy after initial chemotherapy in young children with medulloblastomas and other primitive neuroectodermal tumors. Also, the long-term toxic effects of chemotherapy for young children with medulloblastomas have not been well characterized. Recently, an alarming rate of secondary cancer has been reported in children with malignant brain tumors who were younger than 3 years at diagnosis and were initially treated with chemotherapy.

Atypical Teratoid Tumors

The atypical teratoid tumor is a type of highly malignant neoplasm that has been characterized over the past decade. These tumors contain nests or sheets of rhabdoid cells that have eccentric round nuclei and plump cell bodies. These rhabdoid cells are intermixed with other tumor elements, including regions of primitive neuroectodermal tumor or mesenchymal areas. The rhabdoid areas demonstrate immunohistochemically distinct staining for epithelial membrane antigen, smooth muscle actin, and vimentin. Regions may also stain for glial fibrillary acidic protein, cytokeratin, and neurofilament protein. The outcome of patients with atypical teratoid tumors has been very poor. In a study of 52 children, the median time to progression was 4.5 months, with an overall median survival time of only 6 months. The tumors are resistant to therapy and have a high likelihood of leptomeningeal dissemination early in the course of illness.

Although initially diagnosed only in infants, more recently older patients have been diagnosed. Cytogenetic studies have demonstrated a high incidence of chromosome 22 abnormalities, including monosomy and partial deletions. Given the poor prognosis of patients with such tumors, newer therapeutic approaches are needed. In addition, if in studies evaluating the efficacy of treatment, atypical teratoid tumors are not evaluated separately from other embryonal tumors such as medulloblastomas, conclusions concerning the efficacy of therapy may be misleading.

Glial Tumors

Pediatric glial tumors make up over one half of all childhood brain tumors. Most pediatric glial tumors are low-grade tumors that tend to be most common in the posterior fossa and diencephalic region. The indolent nature of these lesions makes treatment choices difficult, especially for tumors arising in eloquent regions of the brain and in children with minimally symptomatic or asymptomatic tumors such as with neurofibromatosis type 1 having abnormalities consistent with gliomas found on screening magnetic resonance imaging examinations. Alternative means of treatment, including chemotherapy and focused radiation techniques, are increasingly being used in children with low-grade gliomas.

Brainstem Gliomas

Diffuse intrinsic tumors of the brainstem are relatively more frequent in children than adults. Little progress has been made in the management of diffuse intrinsic tumors. Attempts to improve overall survival by increasing the dose of radiation therapy, either by hyperfractionated radiation therapy techniques delivering doses as high as 78 Gy of radiation therapy, or by using alternative radiotherapy techniques, including accelerated hyperfractionated radiation therapy, have not changed the prognosis for children with these lesions. More than 90% of patients will die from progressive disease within 18 months of diagnosis.

The only notable advance in the management of childhood brainstem gliomas is the current understanding that not all childhood brainstem tumors are diffuse intrinsic brainstem gliomas. Approximately 20% will be more focal lesions, usually presenting in a more indolent fashion. Such tumors may arise in the cerebro-medullary region extending exophytically from the brainstem; they may involve the tectum and manifest symptoms of hydrocephalus with a minimal number of other neurologic deficits; or they may focus in the pons causing limited sixth and/or seventh cranial nerve dysfunction. These “focal” lesions are usually pilocytic astrocytomas and carry a much more favorable prognosis, although their management remains controversial. While surgery may result in prolonged disease stabilization, surgical interventions may also cause serious neurologic impairments. Treatment with chemotherapy or focused radiation therapy techniques may result in long-term disease control and less neurologic morbidity.

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Low-grade Gliomas

Although surgical resection is the optimal management of low-grade gliomas, especially pilocytic astrocytomas, because of the location of such tumors surgery is not always feasible. This is especially true in children with dienecphalic tumors, including extensive visual pathway gliomas and hypothalamic lesions. Chemotherapy has primarily been used in younger children, especially those younger than 5 years with extensive lesions where radiation therapy is thought to be relatively contraindicated because of potential long-term radiation-associated brain injury. A carboplatin and vincristine regimen resulted in shrinkage in more than 60% of children and tumor stabilization in another 30% of patients with progressive low-grade gliomas. Because of the success of chemotherapy in halting the growth and often shrinking low-grade gliomas, there have been recent attempts to use chemotherapy in older patients. However, since most patients benefit from chemotherapy for only a finite period, the rationale for using chemotherapy to delay the need for radiation therapy in older patients is less clear. The optimal chemotherapeutic approach for children with low-grade gliomas has not been determined by prospective randomized studies. Intensification of chemotherapy may result in a greater frequency of objective responses to treatment; however, it is unclear whether such responses are predictive of long-term control. In the carboplatin and vincristine study, children who had tumor shrinkage after treatment had the same long-term outcome as those patients who had stable disease after completion of chemotherapy.

Similarly, there has been a great deal of interest in using focused radiation therapy techniques in children with low-grade gliomas. Although such techniques may be effective in controlling disease, the morbidity of high-dose focused radiation techniques in children has not been fully evaluated. Additionally, the long-term benefits of such radiotherapy toward control of the leading edge of the tumor has not yet been determined by prospective studies that follow patients for many years.

The management of children with neurofibromatosis type 1 and low-grade gliomas also continues to be under study. Many children with neurofibromatosis type 1 will have apparent low-grade gliomas on magnetic resonance imaging screening studies performed at a time when they are asymptomatic. Such patients usually undergo follow-up sequential scans and treatment only when there is either clinical or neuroradiographic evidence of disease progression. However, low-grade gliomas in children with neurofibromatosis type 1 are notoriously erratic in their natural history; at times, tumors will seem to undergo a growth spurt and then spontaneously stop growing. This erratic natural history makes treatment decisions and evaluations of the efficacy of treatment quite difficult.

MALIGNANT GLIOMAS

Although the outcome for children with malignant gliomas is poor, the survival rates for children with childhood high-grade gliomas are somewhat better than those for adults with histologically similar tumors. The reasons for this are unclear, but biological differences have been postulated for adult and childhood gliomas, and there is some suggestion that genetic alterations are different in adult tumors compared with childhood tumors.

In one randomized study, the addition of CCNU and vincristine during and after radiotherapy for children with high-grade gliomas improved outcome compared with treatment with local radiation therapy alone. Although the study was performed in a small cohort of patients, the event-free 5-year survival rate in patients treated with radiation and chemotherapy was 43% as compared with 10% for patients treated with radiation alone; surprisingly the differences were primarily seen in children with glioblastoma multiforme. The use of preradiation chemotherapy has not yet been shown to improve survival for children with high-grade gliomas, and in a recently completed prospective study, the use of 8-drug-in-1-day therapy prior to and after radiation therapy was no more effective than vincristine and CCNU given during and after radiotherapy. However, this prospective trial did demonstrate that surgery plays an important role in the management of patients with high-grade gliomas, as patients who underwent total or near-total resections fared better than those who had less aggressive resections.

There has been considerable interest in the use of intensified chemotherapy for children with high-grade gliomas. In one study, high-dose chemotherapy using a thiopeta-based regimen supported by autologous bone marrow rescue demonstrated an impressive 30% long-term disease control rate in children with recurrent malignant gliomas. To my knowledge, these results have not been duplicated by other groups studying high-dose chemotherapy. It is unclear whether the improved survival rate was due to the differences in chemotherapy (as the other studies have not used a thiopeta-based regimen) or were secondary to patient selection (as children with minimal residual disease at the time of diagnosis were the ones who seemed to have the greatest benefit from high-dose chemotherapy). However, no other study, independent of risk factors, has shown as high a salvage rate in patients with recurrent disease.

Given the study results of the thiopeta-based regimen supported by autologous bone marrow rescue, there is considerable interest in attempting to use high-dose chemotherapy with peripheral stem cell support in children with newly diagnosed high-grade gliomas. Once again, patient selection becomes a critical factor because, unlike the usual situation in adults, some children with high-grade gliomas, including glioblastoma multiforme, will have long-term disease control after standard radiation therapy and less aggressive adjuvant chemotherapy. Other approaches under study in children include the use of novel chemotherapeutic agents prior to radiation therapy and the use of chemotherapy during radiation, partially to act as a radiosensitizer.
REFERENCES


