Advances in Treatment of Pediatric Brain Tumors

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Summary: The long-term survival of children with brain tumor has improved considerably in the last three decades, owing to advances in neuroimaging, neurosurgical, and radiation therapy modalities, coupled with the application of conventional chemotherapy. MRI, MR spectroscopy and diffusion-weighted MRI have contributed to more accurate diagnosis, prognostication and better treatment planning. Neurosurgical treatment has been advanced by the use of functional MRI, and intraoperative image-guided stereotactic techniques and electrophysiologic monitoring. The use of 3-D conformal and intensity-modulated radiation therapy, stereotactic radiosurgery, and radiosensitizing agents has made radiation therapy safer and more effective. Conventional chemotherapy, administered either alone or combined with radiation therapy has improved survival and quality of life of children with brain tumors. These improved outcomes have also occurred, due, in part, to their treatment on collaborative national and international studies. Recent promising diagnostic and therapeutic strategies have resulted from advances in understanding molecular brain tumor biology. Important new approaches include the refinement of drug-delivery strategies, the evaluation of biologic markers to stratify patients for optimal treatment and to exploit these molecular differences using "targeted" therapeutic strategies. These approaches include blocking tumor cell drug resistance mechanisms, immunotherapy, inhibition of molecular signal transduction pathways important in tumorigenesis, anti-angiogenic therapy, and gene therapy. The thrust of such approaches for children with brain tumors is especially directed at reducing the toxicity of therapy and improving quality-of-life, as well as increasing disease-free survival. **Key Words:** Pediatric brain tumor, neurosurgery, radiation therapy, chemotherapy, immunotherapy, small molecule.

INTRODUCTION

Central nervous system malignancies are the most common solid tumors in childhood, and are the leading cause of cancer-related death in this age group. Over the last two to three decades, advances in neuroradiologic and other diagnostic/prognostic modalities, neurosurgical and radiation therapy (RT) techniques, and the application of chemotherapy, are responsible for the considerable improvement in the long term survival of children with brain tumors. Yet, a significant proportion still die of their disease. Moreover, in long term survivors, the potential adverse effects of therapy may negatively influence neurologic function and quality of life. Recent advances in molecular and cellular brain tumor biology have resulted in better understanding of tumor classification and biologic staging, and of specific molecular mechanisms of tumorigenesis or resistance to chemotherapy. This knowledge has created new strategies of targeted therapies that exploit differences between neoplastic and normal cells, permitting more effective therapy to be aimed directly at the tumor, while sparing normal tissue, and leading to fewer long term adverse sequelae of treatment. In some targeted therapies, the therapeutic agents are ligands for specific tumor cell surface receptors or antigens not present on normal cells that kill tumor cells by virtue of linkage to toxins or radioisotopes. Others work by blocking specific mechanisms of tumorigenesis, such as tumor angiogenesis or oncogene-altered cellular signal transduction pathways. Other new strategies include forms of immunotherapy and gene therapy. Ongoing and future clinical trials with these novel therapies should continue to improve survival and quality of life of children with brain tumors.

This review will address advances in conventional diagnostic and prognostic modalities (neuroimaging, tumor histopathology and biologic markers) and therapeutic modalities (surgery, radiation therapy, chemotherapy) that have contributed to the improved outcome of children with brain tumors, and present an overview of new investigational therapeutic approaches. Specific current and possible future management strategies for several common pediatric brain

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tumors, including medulloblastoma/PNET, and high-grade and low-grade gliomas, are reviewed.

DIAGNOSTIC/PROGNOSTIC MODALITIES

An accurate diagnosis is of obvious importance in selecting optimal therapy for a child with a brain tumor. The ability to predict the biologic behavior of a tumor is tightly linked to accurately stratifying patients for treatment, to separate those who require more intensive therapy from those in whom less aggressive therapy may be justified without a reduction in survival. Thus, advances in diagnostic and prognostic modalities are integral to progress in the treatment and outcomes of children with brain tumors

MRI/MRS/diffusion MRI. Magnetic Resonance Imaging (MRI) has been paramount in accomplishing the non-invasive diagnosis of brain tumors. Some pediatric brain tumors are so characteristic on MRI, that if they have a clinically typical presentation, no tissue diagnosis is required before treatment, including some optic pathway/hypothalamic gliomas, low-grade tectal midbrain gliomas, and malignant pontine gliomas.[1–3] MRI aids the surgical approach for the majority of tumors which require surgery to establish the histologic diagnosis and reduce tumor burden. MRI can also be coupled to image-guided stereotactic techniques, either for stereotactic biopsy of deep-seated lesions deemed high-risk for resection, or to aid in the approach for an open biopsy and attempt at a more extensive resection. MRI is also of enormous value in tumor-staging. A post-operative brain MRI performed within the first 24-48 hours gives a more accurate assessment of residual tumor volume than was provided by CT. As well, MRIs are more sensitive and easier to perform than myelograms for detecting leptomeningeal spread within the neuroaxis.

Magnetic resonance spectroscopy (MRS). MRS permits the measurement of multiple chemical metabolites in normal and abnormal brain parenchyma; abnormal patterns have been identified in brain tumors.[4] The level of choline and the ratio of choline-to-creatinine, or choline-to-N-acetyl aspartate (NAA) in a lesion correlate with higher cellular proliferation rate, and reflect the presence of a more malignant and rapidly growing tumor. NAA is considered a neuronal membrane marker, which decreases with replacement of neurons by tumor (or other non-neuronal tissue, including necrosis). Decreased choline may represent tissue destruction, reflecting either spontaneous or therapy-related tumor necrosis. In the management of brain tumors, MRS is most valuable in the evaluation of whether MRI changes represent treatment-related effects or recurrent disease; it may also prove useful in the assessment of tumor response to therapy.[5]

Diffusion-weighted MRI. The use of diffusion-weighted MRI is currently being explored to identify parameters of tissue change at a cellular level that might help predict tumor response to therapy.[6] Diffusion-weighted MRI measures the molecular mobility of extracellular water; alterations in water mobility appear to reflect treatment-induced changes in tissue structure. Current understanding is that water diffusion increases acutely in tumors responsive to therapy. This precedes changes in tumor volume. This early indicator of treatment response and outcome before completion of therapy may permit tailoring of treatment in a more timely fashion.[7]

Tumor classification/prognostication

Histopathology. Assessment of the histologic characteristics of a tumor by light and sometimes electron microscopy, is necessary for their diagnosis/classification, and aids in grading the degree of anaplasia for those tumors in which grade is useful for prognosis. The number of tumor mitoses in a microscopic field, the traditional measure of cellular proliferation, also helps assign tumor grade. However, a newer approach to evaluating cellular proliferation employs immunostaining of Ki-67, a nuclear antigen expressed in certain phases of the cell cycle, using the equivalent monoclonal antibody MIB-1.[8] The MIB-1 proliferation index correlates with the biologic behavior and prognosis of low-grade and malignant gliomas in children,[9,10] and in medulloblastomas, where "hot spots" of high proliferation rate were predictive of poor outcome.[11]

Genetic tumor markers. Recently, the detection of molecular genetic traits of pediatric brain tumors is providing new information to classify tumors and predict prognosis. This should translate to more accurate risk-stratification than traditional tumor grading and staging, and ultimately, to better treatment outcomes. Some of the genetic alterations of pediatric brain tumors differ from those of adults. For example, p53 mutations were found in 40% of the malignant gliomas of children older than 3 years, a much higher rate than in the tumors of older adults, but comparable to that in young adults.[12] Such tumors are known as secondary high-grade gliomas, because they contain p53 mutations, which are present in low grade gliomas, subsequently progress to high-grade gliomas accompanied by mutations of other tumor suppressor genes such as the retinoblastoma (Rb) gene or phosphatase and tensin homology (PTEN) gene.[13] Overexpression of p53 in malignant gliomas in children, found in one third of tumors examined, and not always in association with a p53 mutation, was strongly associated with a poor prognosis, independent of tumor histology and clinical prognostic features.[14] Adult high-grade gliomas referred to as de novo (primary) malignant gliomas do not show p53 mutations or overexpression, but rather

tend to show amplification of the epidermal growth factor receptor (EGFR) gene or inhibitor of cyclin-dependent kinase 4 tumor suppressor gene as probable mechanisms of tumorigenesis. However, in high grade gliomas in children, EGFR amplification is rarely seen, although overexpression of EGFR is very common.[15] Because of these differences in the genetic alterations between pediatric and adult pediatric brain tumors, age-specific analysis will be essential in future studies.

For medulloblastomas, genetic markers which have correlated with prognosis in small studies include Trk C (neurotrophin 3 receptor) expression, of which a high level correlated with good outcome[16] and C-myc oncogene amplification, which had very high predictive power of a poor prognosis, though it was only present in 7% of the tumors tested.[17] Other genetic alterations found in medulloblastomas, which may have prognostic predictive value are those of the N-Myc and ERRB2 oncogenes,[18] loss of caspase-8 expression,[19] and mutations of several signal transduction pathways including the PTCH1/"Sonic Hedgehog", Wingless" (WNT/WG)/beta catenin, and PDGF-a/RAS/MAP tyrosine kinase pathways.[20,21] At this time, the best independent predictor of medulloblastoma outcome may be the overall pattern of gene expression. DNA microarray gene expression analyzed in tumor tissue from a large cohort of medulloblastoma patients showed that clinical outcome is predicted by the profile of gene expression, and is a better predictor than the expression or amplification of any single gene or any single gene mutation.[22] The results of the gene expression patterns and other genetic alterations are now being validated in the current Childrens Oncology Group (COG) protocols for medulloblastoma, and may complement clinical and histologic criteria for risk-stratification in future studies.

Mutation of the gene INI-1 on chromosome 22, has recently been detected in a high percentage of patients with the intracranial tumor, the atypical teratoid/rhabdoid tumor (AT/RT).[23] These tumors, which predominate in young children, are frequently mistaken for medulloblastoma or primitive neuroectodermal tumors (PNET) based on histological appearance, but are much more aggressive with a worse prognosis and require more intensive treatment. Therefore, the malignant tumors of children less than 3 years of age should probably be tested for this mutation.

THERAPEUTIC MODALITIES

Surgery. Surgery is the initial treatment for the majority of children with brain tumors. A surgical resection that is as extensive as possible is important for the best long-term survival with most tumors. For some, such as low grade cerebellar astrocytomas, a complete surgical resection is curative. For others, like ependymoma and medulloblastoma, maximal resection confers a better prognosis for survival, even though additional adjuvant therapy, such as chemotherapy and/or radiation therapy, is also required. The extent of resection has to be balanced between the benefit to be gained and the risk of injury to critical neuroanatomic structures. Newer radiographic and electrophysiologic methodologies permit a surgical approach to some previously "unresectable" tumors, with a better margin of safety. Functional MRI allows preoperative determination of the proximity of the tumor to eloquent brain regions. Image-guided stereotactic techniques now permit intra-operative tumor localization and clarify the tumor's relationship to critical structures. Various types of intra-operative electrophysiologic monitoring also optimize the degree of resection while minimizing risk for neurological morbidity. These include the measurement of evoked motor and sensory responses during surgery so that the extent of resection can be limited if critical loss of function is encountered, and electrical corticography, which involves placing subdural electrodes on the surface of brain for "mapping" of vital regions before tumor resection is undertaken.[24]

Radiation therapy. Radiation therapy (RT) was the first adjuvant treatment for brain tumors, and was initially applied to the treatment of adult gliomas and pituitary tumors in the early 1900s. It remains very effective therapy for many malignant pediatric brain tumors, contributing substantially to duration of survival and the chance for cure. RT for pediatric brain tumors is usually delivered either to the primary tumor site (involved field) or to the entire craniospinal axis for tumors such as medulloblastoma with an underlying tendency to metastasize throughout the central nervous system.

With the improved survival of children with brain tumors over the last two decades, in part due to advances in the delivery of RT, recognition of its adverse effects on the developing nervous system has increased. Radiation-mediated neurologic "late effects" include the potential for cognitive impairment, CNS vasculopathies and stroke, neuroendocrine deficits, and increased risk for secondary malignancies in the radiation field, all of which are magnified in younger children.[25]

The use of RT for tumors is predicated on a differential effect on tumor vs. normal tissue, the therapeutic ratio.[26] Substantial improvements in RT for brain tumors have arisen from development of technologies that optimize this ratio by maximizing therapeutic dose to tumor while minimizing dose to surrounding normal brain. Three-dimensional conformal RT and intensity-modulated RT have come about through better computer modeling capabilities linked to improved imaging and the delivery of RT through multiple portals. This permits more precise tailoring of RT dose to irregular tumor contours and reduces its administration to surrounding brain.[27] The detrimental effects of RT are now somewhat decreased

with the widespread implementation of these technologies.

Stereotactic radiosurgery and the Gamma knife are RT approaches that entail delivery of a single high dose of radiation using a large number of intersecting beams, and facilitated by precise neuroimaging and cranial immobilization. These methods have been useful for the treatment of unresectable pediatric brain tumors which are small and well circumscribed, and where the ablation of normal tissue very close to the target does not cause unacceptable toxicity.[28] Another recent experimental approaches to improve the efficacy of RT is the use of biologic response-modifiers that increase tumor sensitivity to radiation or decrease radiation resistance. Pretreatment with chemotherapeutic agents, such as carboplatin and gemcitibine were found to enhance the effect of irradiation on tumor cell killing.[29,30]

Chemotherapy. Chemotherapy for the treatment of pediatric brain tumors was initiated in the 1970s and its use is still driven by the relatively poor prognosis of many of these neoplasms, as well as by concerns about the detrimental adverse effects of RT on the developing brain. With conventional chemotherapeutic agents alone or in combination with RT, there has been considerable improvement in the outcome of children with brain tumors, including medulloblastoma, malignant astrocytoma, low grade optic pathway glioma, and malignant tumors in infants. A pivotal factor in improvement in the treatment of may pediatric brain tumors, is the high level of participation in trials conducted through multi-institution consortia such as the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG), now merged as the Children's Oncology Group, The International Society of Paediatric Oncology (SIOP) and the Pediatric Brain Tumor Consortium. Participation in such clinical trials is critical for therapeutic advances to continue. Specific chemotherapy regimens are discussed below.

Investigational therapies: Overview. Identification of molecular disparities between brain tumor cells and normal cells has opened the way for a number of therapeutic strategies that exploit these differences. Unique properties of tumor cells may permit the targeting of tumor cells for elimination, while sparing normal cells. Such "targeted" therapies inhibit tumor growth by various approaches, including immunotherapy, inhibition of signal transduction pathways, anti-angiogenic therapy, and regulation of gene expression.

Immunotherapy. Advances in basic immunological research have stimulated interest in immunotherapy as a modality for targeted treatment of brain tumors. Two promising immunotherapeutic approaches are the development of various tumor vaccines, and of monoclonal antibodies or other ligands for tumor-specific receptors that can be linked to tumor toxins or radioisotopes.

Vaccine therapy employs strategies for activating the immune system to overcome the tolerance that appears to develop to cancer cells. Dendritic cells, the most potent antigen-presenting cells, can be sensitized with various forms of tumor antigen to induce stronger cell-mediated active immune responses that inhibit the growth of human gliomas in both adults and children.[31,32] In animal models, T-cell-activating cytokine genes have been introduced into autologous irradiated tumor cells ex-vivo, and these cells are then used for vaccination to override tumor-induced immunosuppression.[33]

Monoclonal antibodies to a number of tumor growth factors or to growth factor receptors, such as epidermal growth factor (EGF) and its receptor (EGFR), among others, have tumor cell anti-proliferative activity in vitro and in animal xenograft models. Results from ongoing phase I and phase II brain tumor clinical trials using armed radio-labeled monoclonal antibodies, targeting various tumor-specific antigens are somewhat encouraging, with stabilization of disease and prolonged survival, although many challenges to its safe and effective application for brain tumors remain.[34]

Ligands for tumor-specific receptors may also effectively target brain tumors. Transferrin receptors are much more numerous on both glioma and medulloblastoma tumor cells than on normal cells. In *in vivo* animal models, transferrin conjugated to Diphtheria selectively binds to and kills tumor cells.[35] This methodology has shown promising results in an adult clinical trial, with significant responses of recurrent malignant gliomas after intratumoral injection of the transferrin/diphtheria toxin conjugate.[36] It is currently being tested in recurrent supratentorial high-grade gliomas in children.

Inhibition of tumor signal transduction pathways. Another targeted therapy involves the inhibition of specific molecular pathways important for tumor growth. Tumor cell growth factor receptors are linked through complex downstream molecular pathways involved in cellular proliferation. Some monoclonal antibodies directed against such receptors can inhibit these signal transduction pathways and promote tumor cell apoptosis. Other small molecule inhibitors directed against tumor cell receptor tyrosine kinases may be important tumorigenic mechanisms in some medulloblastomas and high-grade gliomas. These include gefitinib (Iressa) targeting the epidermal growth factor receptor (EGFR) tyrosine kinase,[13] imatinib mesylate (Gleevec), targeting the platelet-derived growth factor-alpha receptor (PDGFaR) tyrosine kinase, [21] and erlotinib (Tarceva), targeting the oncogene ERBB2 receptor tyrosine kinase.[13] These small molecule inhibitors have entered clinical brain tumor trials for adults and children.

Agents directed at downstream targets in other tumor proliferation signal transduction pathways are also in development, including those directed against the PTCH/

Sonic Hedgehog pathway, important in some medulloblastomas.[37] Inhibitors of the PTEN oncogene-activated phosphatidylinositol-3 kinase/ras/AKT and downstream target, mammalian target of rapamycin (mTOR) pathway (PTEN/PI3K/ras/AKT/mTOR pathway), such as rapamycin (Sirolimus) and rapamycin derivative (Everolimus) are important in the tumorigenesis of some high-grade gliomas and are in adult clinical trials.[13] Farnesyl transferase inhibitors, such as tipifarnib (Zarnestra), which impair processing of proRas and inhibit the Ras signaling pathway, are also now in clinical trials for pediatric and adult brain tumors.[13]

Anti-angiogenic therapy. Tumor-induced angiogenesis is a process discovered to be an important mechanism supporting tumor growth in several models.[38] Angiogenic factors such as α *and* β fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), and angiogenin, among others, are elaborated by tumor or mobilized from extracellular matrix or macrophages drawn to tumor under the influence of hypoxia, and facilitate angiogenesis in a number of ways.[38] Anti-angiogenic agents have diverse mechanisms of action; they may inhibit endothelial cell proliferation, inhibit specific angiogenic factors, target vascular smooth muscle or integrin signaling, or inhibit matrix metalloproteinases. Some have produced tumor regression and cure in animal tumor xenograft models.[39] Phase I clinical trials of anti-angiogenic agents are underway.[38] Cilenglitide (EMD 121974), an anti-angiogenic integrin receptor antagonist in preclinical trials,[40] is currently being evaluated in a phase I trial for children with recurrent brain tumors. Preliminary results suggest some efficacy for brain tumors; a likely future strategy will be to combine anti-angiogenic drugs with other adjuvant therapies.

Gene therapy. Increased understanding of the molecular events in tumor development may permit the application of gene therapy strategies to the treatment of both adult and pediatric brain tumors. Gene therapy offers the hope of sensitizing tumor cells to systemic therapies, replacing defective tumor genes, and blocking mechanisms of tumor progression. This may be accomplished using various vector and delivery systems. Types of vectors most suitable for tumor gene therapy include retroviral, herpes, and adenoviral and adeno-associated vectors.[41] Retroviral vectors preferentially infect rapidly dividing cells which, in theory, would make them good candidates to treat malignant brain tumors; goals include maximizing transfection of tumor cells and minimizing transduction of normal cells.

Delivery of the transfected gene to the tumor is achieved either by direct intra-parenchymal installation or by intravascular delivery. Intra-parenchymal delivery provides more accurate localization to the tumor, but encounters problems of failure of diffusion of the gene to all of the tumor cells. Intravascular delivery to the brain has the obvious difficulties of traversing the blood-brain barrier, possibly overcome by disruption of the barrier at the time of delivery, as well as the lack of localization and greater possibility for interaction with non-target cells, such as endothelial cells.

Several gene therapy strategies for brain tumors are currently being applied, mainly to adult populations, and may have potential for application to the treatment of pediatric brain tumor in the future; These include prodrug activation, tumor suppressor gene therapy, and antisense gene therapy.[41]

Prodrug activation. Prodrug activation is also termed "suicide therapy," in which a vector carrying a gene coding for a protein that sensitizes cells to a specific drug is delivered to a tumor. The largest experience with this type of therapy uses the herpes simplex virus thymidine kinease-gancyclovir regime to treat malignant gliomas. In this model, a modified herpes virus vector expressing the enzyme, thymidine kinase, after stereotactic intratumoral injection, is preferentially taken up and encorporated by rapidly dividing tumor cells.[42] The patient is given gangcyclovir systemically, which is then converted by the thymidine kinase to a toxic metabolite, killing the tumor cells. Unfortunately, this regimen, which has been tried in children with high-grade gliomas, has so far met with limited clinical success, mainly because of poor transfection efficiency of tumor cells.[43] There are ongoing studies with several other prodrug activator proteins and their corresponding prodrugs that may provide more powerful combinations for gene therapy in the future.[44]

Tumor suppressor gene therapy. Tumor suppressor genes code for proteins that inhibit cell growth. The loss of tumor suppressor function by mutation or deletion of a tumor suppressor gene has been implicated as the mechanism of oncogenesis of glioma and medulloblastoma brain tumors.[45] Tumor suppressor gene therapy replaces the missing or mutated tumor suppressor protein, theoretically restoring the normal pre-tumor cell phenotype. Preclinical animal studies applying this therapy for the p53 and PTEN tumor suppressor genes encouraging, but tumor heterogeneity in human tumors, with cells in the same region expressing different genes, is an obstacle to using this paradigm, clinically.[46]

Antisense gene therapy. Antisense gene therapy prevents the expression of proteins that facilitate tumor progression. Knowledge of the oncogene DNA sequence responsible for a protein important for tumorigenesis, allows design of a vector with the "antisense" gene that will produce a single-stranded RNA molecule with a sequence complementary to the mRNA produced by the abnormal tumor target gene. When the antisense gene is taken up and expressed in the tumor, the complementary RNA produced then binds to mRNA of the tumor target gene, hindering the ribosome apparatus, preventing mRNA translation and synthesis of the pathogenetic pro-

tein. Using this method, several genes have been inhibited in animal models, such as urokinase plasminogen activator receptor and cathepsin B, resulting in some tumor regression.[47] This methodology should have several advantages over other gene therapy methods, including not being hindered by low transfection rates and having the possibility of inhibiting multiple pathogenetic genes within the same vector. A disadvantage is the relative instability of the single stranded antisense RNA.

COMMON PEDIATRIC BRAIN TUMORS AND THERAPY ADVANCES

Primitive neuroectodermal tumor (PNET)/ medulloblastoma

Central nervous system (CNS) PNETs are a group of malignant primary brain neoplasms composed of primitive undifferentiated neuroepithelial cells with aggressive embryonal characteristics, sometimes with evidence of differentiation along neuronal, glial or ependymal lines. The term PNET was first used to describe supratentorial cerebral hemisphere tumors, but Rorke later proposed that medulloblastoma was the infratentorial (cerebellar) counterpart of these tumors, which she thought should all be grouped together, based on their similar appearance, with small, round, blue undifferentiated-looking cells and presumed common pleuripotential neuroepithelial cell of origin.[48] Though widely accepted, this is not a universal opinion, and while these tumors do have similarities in microscopic appearance and in their proclivity to metastasize throughout the CNS, supratentorial PNETs respond less well to therapy and have a poorer prognosis than their infratentorial/ medulloblastoma counterparts. For this reason they are assessed separately in most therapeutic studies, although the supratentorial PNETs are usually treated on the same protocols as are high-risk medulloblastomas. Recent significant advances made in identifying key molecular markers/gene expression patterns of theses tumors should help to resolve controversy about PNET classification and better stratify them for future therapy.[22]

Medulloblastoma, (infratentorial or cerebellar PNET), accounts for 20-25 % of pediatric brain tumors, making it the most common intracranial tumor of childhood.[49] In children, the tumor typically arises from the cerebellar vermis in the roof of the fourth ventricle into which it grows, filling the cavity and causing obstructive hydrocephalus. (Figure 1) Most children present with symptoms of increased intracranial pressure, including headache, vomiting, irritability or lethargy, and sometimes with symptoms due to involvement of local structures, such as ataxia, head tilt or cranial nerve palsies. Medulloblastoma have a high propensity to CNS dissemination. This dictates that even after a total surgical resection, some type of adjuvant therapy to the entire neuroaxis is required to treat what is very likely to represent invasive multicentric disease.

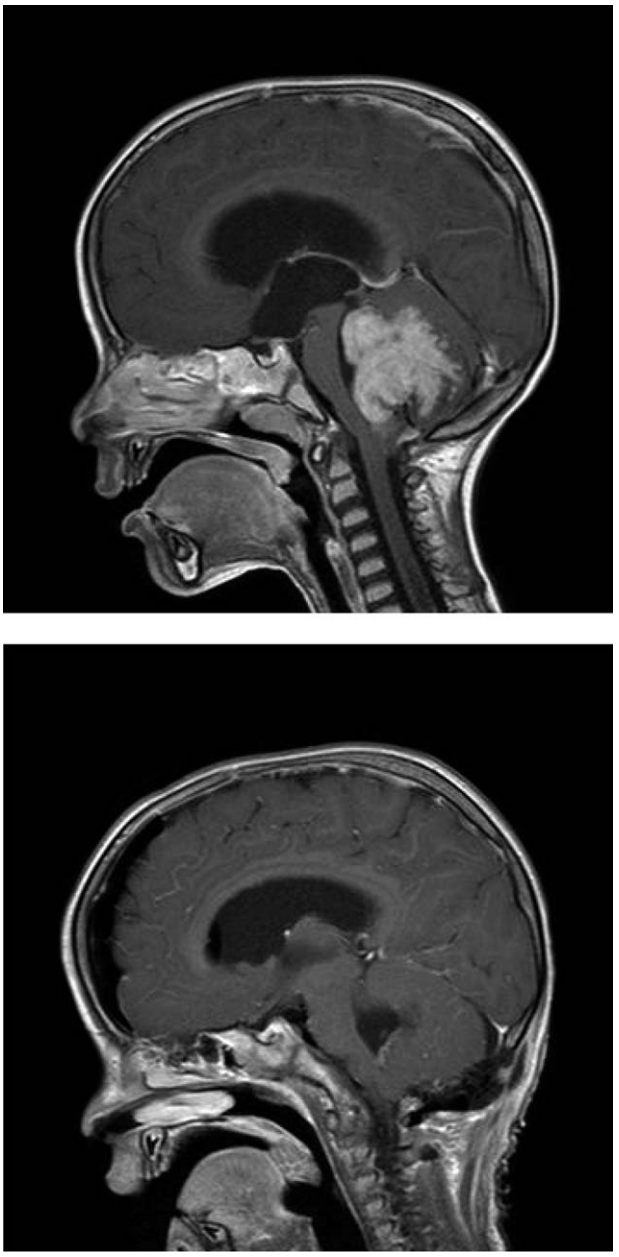

FIG. 1. Sagittal T1-weighted brain MRI, after gadolium administration: a. posterior fossa medulloblastoma before surgery, demonstrating homogeneous enhancement, filling the fourth ventricle and causing obstructive hydrocephalus. b. post-operative image 24 hours after surgery, confirming gross total resection of the tumor.

Contemporary staging of medulloblastoma depends on both a surgical and post-operative MRI estimate of residual tumor at the primary site, on pre-operative or post-operative MRI evaluation of the brain and total spine for metastatic disease, and on the post-operative cytologic evaluation of lumbar CSF. Children with medulloblastoma stratify as high-risk for relapse if they have either metastatic disease in brain, spine or CSF, or

have >1.5 cm^2 residual tumor at the primary site.[18] This risk-stratification scheme currently dictates the therapy regimen employed, in which high-risk medulloblastomas are grouped with supratentorial PNETs because they are at somewhat similar higher risk for recurrence.

Supratentorial PNETs, including pineal regions PNETs, also occur predominantly in early childhood, and are diagnosed by 10 years of age in 80% of patients.[50] They constitute only about 3% of all pediatric brain tumors. Cerebral PNETs may present with signs of increased intracranial pressure, usually from the mass of a large tumor, and/or localizing signs dependent on tumor location. Pineal region PNETs, like other pineal region tumors, often present with hydrocephalus due to compression of the cerebral aqueduct, or with Parinaud's syndrome (upgaze paralysis, absent pupillary reactivity to light, and convergence or retractory nystagmus) from tectal midbrain compression. Supratentorial PNETs also have a propensity to CNS dissemination, and therapy for these tumors, as for medulloblastomas, includes surgery, neuroaxis irradiation, and chemotherapy. The survival rates for children with supratentorial PNETs are poorer than for those with medulloblastoma, but they have been grouped with high-risk medulloblastomas for treatment stratification.

Medulloblastoma/PNET therapy. Surgical resection of the tumor is first line of therapy for medulloblastoma/PNET. Surgery plays an important immediate role in reducing tumor burden, and often in opening the ventricular system, re-establishing normal CSF flow and ultimately obviating shunt placement. Moreover, among medulloblastoma and supratentorial PNET patients with no metastatic disease, there is evidence suggesting that extent of residual tumor after surgery correlates with outcome.[51,52] However, surgical resection, alone, cannot cure medulloblastoma, and radiation therapy to only the primary tumor site, or at a dose of <5000 cGy to the primary site, is associated with poor outcomes. Thus, for some time, standard therapy for medulloblastoma after surgical resection, had been craniospinal irradiation (35-36 Gy) and a boost to the posterior fossa (54-56 Gy), with 5-year progression-free survival (PFS) of about 60%.[18] Although this approach had a major impact on survival, it was far from satisfactory, considering the significant morbidity of craniospinal RT, death from progressive disease in 30-40 % of average-risk patients, and less than 30% survival of those with high-risk disease. Supratentorial PNETs may have an even poorer prognosis after surgery and RT, with a 5-year PFS in one series, of only 12%.[50]

High-risk medulloblastoma/PNET therapy. All these factors were an impetus for medulloblastoma/PNET therapy trials combining RT and chemotherapy. Several trials demonstrated efficacy of adjuvant chemotherapy for high-risk metastatic or residual disease.[53–55] Especially promising results were reported for high-risk medulloblastoma patients using an adjuvant regimen of cisplatin, CCNU and vincristine after standard neuroaxis irradiation, with a 5-year PFS of 85%.[56] Patients who were high-risk due to residual disease did better than those with metastatic disease, with 90% 5-year survival vs. 67%, respectively. Another approach to high-risk medulloblastoma/PNET is the administration of high-dose chemotherapy after craniospinal irradiation. A small international consortium treated 19 high-risk medulloblastoma/PNET patients after RT, with 4 tandem cycles of high-dose chemotherapy with stem cell support, and reported 84% 2-year PFS from the start of radiation therapy.[57]

High-risk supratentorial PNETs, generally, have not done as well as high-risk medulloblastomas. Patients with these tumors treated on the cisplatin/CCNU/vincristine regimen, with craniospinal RT up-front, fared more poorly, with 37% 5-year PFS compared with 67% for high-risk medulloblastoma.[58] Some studies have demonstrated a benefit from chemotherapy for supratentorial PNETs. Dirks et al showed a trend to longer survival in those supratentorial PNET patients who received chemotherapy vs. those who did not.[50] Infants with non-pineal PNETs treated on the "Baby POG" studies had very good 5-year PFS of 55%, but with no benefit for pineal PNET.[25] Recently completed CCG trials for high risk PNET/medulloblastoma studied the use of further dose-intensification of chemotherapy in 3 tandem cycles, with stem cell support after RT, or of chemoradiotherapy using carboplatin as a radiosensitizer for high-risk medulloblastoma/PNET. The results of these studies are pending.

Average-risk medulloblastoma therapy. The improved outcome of high-risk medulloblastoma patients gave momentum to efforts aimed at minimizing treatment-related neurotoxicity in children with average-risk medulloblastoma by reducing craniospinal radiation dose and supplementing the treatment regimen with chemotherapy. Previous attempts at neuroaxis radiation dose-reduction without other adjuvant therapy, had failed when the dose was reduced to 18 Gy, or even to 24 Gy.[59,60] Several subsequent studies showed outcomes of at least 70% PFS with the addition of chemotherapy to craniospinal axis dose of 24 Gy.[61,62] From a pilot study using the regimen of cisplatin/CCNU/vincristine after 24 Gy RT dose to the neuroaxis, children with average-risk medulloblastoma had a 3-year PFS of 85%.[56] In the most recent COG study, after treatment with 24 Gy craniospinal RT and concurrent weekly vincristine, children with average-risk disease were randomized to two different adjuvant chemotherapy regimens (cisplatin/CCNU/vincristine vs. cisplatin/cyclophosphamide/vincristine), each of which resulted in 4-year PFS rates of greater than 80%.[63]

Infant medulloblastoma therapy. Infants and very young children with medulloblastoma have poorer survival than older children when treated with standard RT, and even more significantly, they sustain much greater treatment-related neurotoxicity. Therefore, in the mid-1980s, Duffner et al.,[25] through the Pediatric Oncology Group, developed and implemented a novel approach in which prolonged postoperative multi-agent chemotherapy was given in an attempt to delay radiation therapy for infants less than 3 years of age with medulloblastoma (other infant malignant brain tumors were also included). This approach proved to be successful in delaying RT for as long as 2 years in those youngest at diagnosis, and even in reducing the dosage of neuroaxis irradiation to 24 Gy in children with no evidence of disease after chemotherapy. Although the overall survival rate of 40% at 5 years was poorer than for older children with average-risk medulloblastoma who receive RT upfront, among infants who had a surgical gross total resection (GTR), 5-year survival was 60%, and in those with no metastases at diagnosis and a GTR, it was 69%, comparable to that average-risk patients treated initially with RT. Children's Cancer Group conducted an infant brain tumor study that similarly delayed RT in infants $<$ 3 years, using prolonged "8-in-1" chemotherapy, but with a 3-year PFS of only 22%, (likely because this chemotherapy was less intensive), although most of these long-term survivors, in fact, never received any RT.[64]

A different approach with the goal of deferring RT until relapse was pursued in several small trials using various different chemotherapy regimens; outcomes ranged from 5-year survival of 67%, to 2-year survival of 43%.[65–67] The results of the French Oncology Group (SFOP) study of children $<$ 5 years old treated for 16 months with multiagent chemotherapy and deferring RT until relapse, emphasized the importance of radical surgery; the 5-year PFS of the 34 children with no metastatic disease (M0 stage) and GTR was 41% vs 0% for those with a subtotal resection.[68] Taken together, these studies suggest that infant medulloblastomas are responsive to chemotherapy, and that a gross total resection and M0 staging are significant prognostic factors. Such infants could reasonably be treated with relatively-prolonged chemotherapy, withholding RT until relapse; those with metastatic or residual tumor require a different approach.

A recently conducted trial, CCG 99703, tested an hypothesis that intensifying the chemotherapy while deferring RT, would improve outcome for infant medulloblastoma patients $<$ 3 years of age. This study employed three cycles of chemotherapy similar to the initial "Baby POG" regimen, followed by three cycles of dose-intensified (but subablative) chemotherapy, with carboplatin and dose-escalation of thiotepa, supported with autologous stem cells collected after the initial cycles of chemotherapy; no RT was prescribed or specifically recommended. The study closed to accrual in late 2004 so that outcome results are pending.

Also, because of concern for neurotoxicity of RT in young children, the use of high-dose ablative chemotherapy with autologous bone marrow transplant (ABMT) or stem cell rescue for children with recurrent or newly diagnosed tumor is being explored. In view of the chemo-sensitivity of medulloblastomas there have been preliminary studies in which a small number of newly-diagnosed infants were successfully treated in consolidation with high-dose chemotherapy followed by bone marrow or stem cell support; this approach may have a larger role in treating young children, as it may for patients who relapse after standard therapy.[69,70]

Because of the high risk for development of neurocognitive deficits and the moderate success using chemotherapy, there has been little enthusiasm for administering RT, especially in a craniospinal volume, to infants and children $<$ 3 years of age. However, the possibility of using RT for local tumor control is being re-considered for infants, in view of the availability of the newer focused or 3-D conformal radiation. This approach is currently being used for infants with M0 medulloblastoma in COG study 9934; infants receive 3-D conformal RT after multiagent induction chemotherapy (and a second surgery for residual after chemotherapy), followed by 8 additional months of maintenance chemotherapy. Moreover, this conformal approach is being applied to primary site radiation therapy for average-risk medulloblastoma in older children, also aimed at reducing the neurotoxicity of brain irradiation. The methodology facilitates the accurate delivery of the tumor bed-radiation boost, with significant reduction in the radiation scatter to normal brain structures including the cochlea and auditory nerve in the posterior fossa, as well as to the diencephalon and other portions of supratentorial brain. Two single institution pilots have already demonstrated safety of this technique, with no increased posterior fossa recurrences among patients.[71,72] These findings are being validated in the current COG average-risk medulloblastoma study, which randomizes patients to conformal tumor bed with margins volume vs standard posterior fossa volume.

Medulloblastoma/PNET investigational therapy. Better therapy for medulloblastomas undoubtedly will have its basis in clarification of tumor molecular biology, and could evolve in at least two ways. Improved understanding of the molecular signature of individual tumors will help in determining prognosis and more accurate tumor risk-stratification, permitting children at lower risk for recurrence to safely receive less toxic therapy, and reserving more intensive treatment for those at higher-risk. Knowledge of the molecular defects critical in tumorigenesis could also provide the means to use them as targets for novel therapeutic approaches.

A number of studies have identified several possible molecular traits that could serve as prognostic factors, as well as potential targets for therapy of medulloblastoma. Among these are the amplification or overexpression of several oncogenes, including ERBB2, C-Myc, and N-Myc,[18] loss of caspase-8 expression,[19] and mutations in several other signal transduction pathways including the PTCH1/"Sonic Hedgehog" pathway, "Wingless" (WNT/WG)/beta catenin pathway,[37] and platelet-derived growth factor-alpha (PDGF-a) and RAS/MAP tyrosine kinase pathway.[21] The best outcome predictor, to date, appears to be tumor gene expression profiling. A pilot study of medulloblastoma DNA microarray gene expression was able to demonstrate that clinical outcomes of children with medulloblastoma was highly predictable on the basis of the gene expression profile of their tumors at diagnosis, and independent of clinical or other criteria.[22] The prognostic accuracy of any of these molecular markers in medulloblastoma is not yet firmly established, as they have all been evaluated in somewhat underpowered studies or have included heterogenous patient groups. However, validation of the most promising of these markers is ongoing in current COG and other international consortia medulloblastoma studies.

Understanding mechanisms of tumorigenesis for future molecular classification and prognosis is also the first step in the development of molecular-targeted therapies. Specific small molecule tyrosine kinase inhibitors could prove effective against targets in some medulloblastoma (and other brain tumors). These include imatinib mesylate (Gleevec), a PDGFa/RAS/MAP tyrosine kinase inhibitor,[21] Erlotinib (Tarceva), which inhibits the oncogene, ERBB2 tyrosine kinase, and Iressa (gefitinib), which inhibits the EGFR tyrosine kinase.[13] Molecular-targeted therapies still in pre-clinical evaluation include cyclopamine, a plant-derived teratogen that suppresses the membrane protein, SMO, which is activated and stimulates cell proliferation when there are mutations in the PTCH/Sonic Hedgehog pathway of some medulloblastomas;[20] cyclopamine has side effects that limits its clinical application, but other agents which inhibit this pathway are also under development.

The retinoid, cis-retinoic acid, is another therapeutic agent soon to be evaluated in a randomized fashion in the upcoming COG protocol for high-risk medulloblastoma/PNET tumors. Retinoids mediate apotosis in medulloblastoma cells in vitro, and suppress tumor growth in xenograft models.[73]

Gliomas/Astrocytomas

Gliomas, which are predominantly astrocytomas, make up the largest fraction of pediatric primary brain tumors, representing between 45% and 60% of tumors in most series.[49] The majority are low-grade astrocytomas (35-50% of all pediatric brain tumors), in contrast with trends in adults in whom high-grade astrocytomas and glioblastoma are the most common tumors. In the posterior fossa, low-grade astrocytomas are almost always pilocytic astrocytomas, usually in the cerebellar hemispheres, and constitute about 12-15% of pediatric brain tumors.[49] Supratentorial low grade astrocytomas (30-35% of pediatric brain tumors) arise in the cerebral hemispheres (20-25%) or in the midline as optic pathway or hypothalamic gliomas (10%). Only about 10-12% of pediatric brain tumors are high grade astrocytomas, either anaplastic astrocytoma or glioblastoma multiforme, and nearly all in supratentorial locations.

Low-Grade Gliomas. Pilocytic astrocytomas are the second most-common tumor in the posterior fossa after medulloblastoma (12-15% of pediatric brain tumors), and when treated with surgical resection alone, have the best prognosis of any pediatric intracranial neoplasm. Cerebral low-grade gliomas can be pilocytic astrocytomas, but are more often non-pilocytic gliomas of various types; they have greater propensity to infiltrate surrounding brain, which makes performing a complete resection more difficult. Nevertheless, among patients who undergo total resection, 10-year survival rates exceed 80% for hemispheric cerebral tumors,[74] and 90% for cerebellar tumors.[3,75] For tumors that progress following surgery, radiation therapy is beneficial,[76] although there is less experience using it in this setting than there is for the usually unresectable deep midline low grade gliomas discussed below.

In contrast to cerebellar or cerebral low grade gliomas, the midline optic pathway/hypothalamic gliomas (OPG), which constitute 3-5% of pediatric brain tumors and are also frequently low-grade pilocytic astrocytomas, are rarely amenable to complete resection, by virtue of their infiltration of critical structures. These tumors of the visual pathways may involve one or more optic nerves, the optic chiasm (where they may be exophytic into the third ventricle or hypothalamus), the optic tracts, optic radiations, and the occipital cortex (Figure 2). They predominate in young children (75% in those $<$10 years) and are associated with Neurofibromatosis Type 1 (NF 1); 20-30% of OPGs are in NF 1 patients.[77] In lesions that are exophytic from the chiasm into third ventricle or hypothalamus, a subtotal resection may be possible, sometimes obviating a shunt in patients with hydrocephalus.[78] However, for most of these tumors, if treatment is required, alternatives to surgery are necessary.

Although OPG neoplasms nearly always have low-grade histology, their biologic behavior and growth characteristics, in vivo, vary tremendously. Good prognostic factors for stability after diagnosis include involvement only of visual structures and not of hypothalamus, older age of the child, and occurrence in a patient with NF1.[78,79] The treatment of these tumors must be individualized; children with minimal and non-progressive

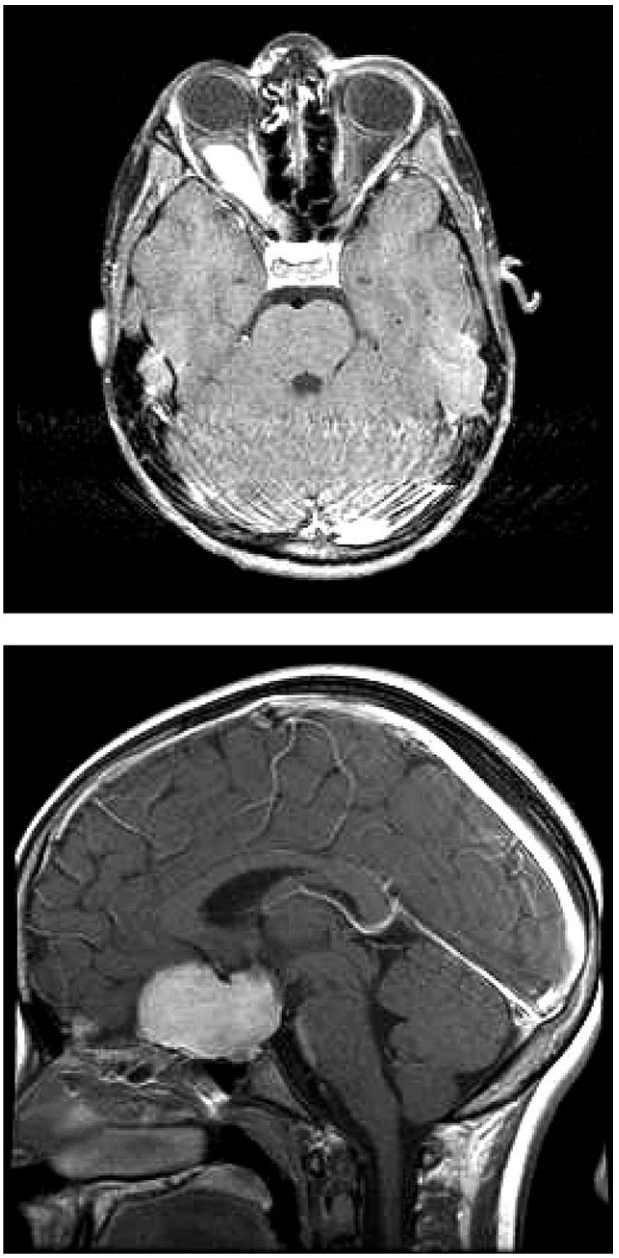

FIG. 2. Axial T1-weighted brain MRI after gadolinium administration, demonstrating enhancing right optic nerve glioma. b. Sagittal T1-weighted brain MRI of an enhancing optic nerve/chiasm glioma that is exophytic into the hypothalamus.

symptoms and radiographic stability, are followed expectantly. Although radiation therapy had been the mainstay of treatment of these tumors,[80] because of the association of radiotherapy with increased risk for neurocognitive and neuroendocrine late effects, especially in children younger than 5 years,[81] currently, RT is usually withheld in favor of administering chemotherapy in an attempt to defer, if not obviate RT altogether. Several chemotherapy regimens including carboplatin alone, carboplatin/vincristine, and procarbazine/CCNU/vincristine/6-thioguanine have been tried for incompletely resectable low-grade gliomas in any location, although the majority are OPG/hypothalamic gliomas. These pilot trials reported regression or stability of tumors in 75-90% of patients.[82–84] At follow-up, children treated on the carboplatin/vincristine regimen before age 5 years, had a 75% 4-year PFS rate.[85] The outcome of a recently-closed COG phase III randomized trial comparing the latter two of these regimens is pending.

Although there are no prospective randomized trials evaluating radiotherapy for low-grade gliomas in children, benefit was reported for 24 children with progressive optic chiasm gliomas, who had 88% 6-year PFS.[80] When radiotherapy is indicated for the treatment of an OPG (or a low-grade glioma in any location), the current strategy of stereotactically-guided conformal radiotherapy is optimal. Results of two studies using conformal RT to treat children with low grade gliomas are encouraging (in 38 children, a 2-year PFS of 88%; in 14 children, a 3-year PFS of 87%).[86,87]

High-Grade Glioma/Astrocytoma

Malignant Pontine Gliomas. The majority of brainstem gliomas are malignant, diffusely infiltrative tumors centered in the pons, and are not resectable. They present with the triad of rapidly progressive cranial nerve deficits, long-tract signs and ataxia, but without hydrocephalus, at a peak age of 5-14 years. Taken together with this typical clinical history, their appearance, with diffuse enlargement of the pons on MRI, is diagnostic, and biopsy is no longer indicated.[3] Unfortunately, the prognosis of these rapidly growing, highly malignant tumors is very poor. The foundation of treatment has been radiation therapy, but the median survival is less than one year. Attempts to improve survival using hyperfractionated RT [88], or chemotherapy [89] have not been successful. A current therapy strategy is the application of chemotherapeutic agents as radiosensitizers, to try to improve the outcome for these tumors.[90]

Supratentorial High-Grade Gliomas. Supratentorial high grade gliomas in children include mainly anaplastic (malignant) astrocytomas and glioblastoma multiforme, and comprise 10-12% of CNS tumors in children. These include cerebral hemispheric tumors, as well as deep midline thalamic tumors.[49]

Supratentorial High-Grade Glioma Therapy. Conventional treatment for cerebral high-grade gliomas has been maximal resection followed by involved-field radiation therapy. Greater extent of tumor resection has been shown to correlate with longer PFS and is the most important clinical prognostic factor for these tumors.[91] Radiation treatment of high-grade gliomas in children has been part of all published treatment regimens of the last two decades, although the data supporting its prognostic value are derived mainly from adult studies. Evidence for improved outcome with adjuvant chemother-

apy for high-grade gliomas in children is modest, but it is routinely used. From one phase III CCG 921 study of children with high-grade gliomas, the 5-year event-free survival (EFS) for those who received adjuvant chemotherapy with the nitrosourea-based regimen of CCNU/vincristine/prednisone plus RT after surgery was 46%, vs.18% for those who received radiotherapy alone. The benefit of the chemotherapy was demonstrated in the 33 children with glioblastoma in whom the 5-year EFS was 42 % for those treated with chemotherapy plus RT vs. 6% for those treated with RT alone, whereas the number of anaplastic astrocytomas in the study was too small to demonstrate an effect of chemotherapy.[92] The other phase III study, CCG 945, for pediatric high-grade gliomas compared two chemotherapy regimens, the prior CCNU/vincristine/prednisone regimen vs. the eight-drugs-in-one-day regimen, for which the overall 5-year EFS rates of 26% vs. 33%, respectively, did not differ.[93] A phase II German trial for pediatric high-grade gliomas determined that the pre-radiation and post-radiation chemotherapy significantly benefited those patients who also had a gross total resection, with 5.2 year vs. 1.9 year median survival.[94]

Other chemotherapeutic agents, such as temozolomide, an orally administered alkylating agent, and irinotecan, a topoisomerase-I inhibitor have been tried for newly diagnosed high-grade gliomas with modest success.[95] A very recently completed phase II COG trial used temozolomide administered daily, concurrent with radiation therapy, and then afterward, in monthly cycles. Other studies combining various agents are also ongoing or in development in the COG.

Supratentorial High-Grade Glioma Investigational Therapy. Some investigational approaches to treatment of high-grade gliomas with chemotherapy focus on circumventing mechanisms of drug resistance that develops to alkylating agents. One of the major mechanisms of resistance to the nitrosoureas is the overexpression of the cellular enzyme in tumor cells, O^6 guanine alkylguanine alkyltransferase (AGAT), which is responsible for removing alkyl groups from the O^6 position of deoxyguanosine and preventing DNA cross-links.[96] The drug O^6 benzyl guanine (O^6 BG) which has high affinity for AGAT, enhances the activity of nitrosoureas in vitro and in vivo.[96] Several phase II trials with O^6 BG and temozolomide, which also has the AGAT drug-resistance mechanisms, are ongoing.

Because the blood brain barrier (BBB) may be an obstacle to delivery of effective chemotherapy to brain tumors, various tactics have been developed to circumvent this problem. One strategy has been the use of agents, such as mannitol, prostaglandins, histamine and bradykinin, capable of transiently disrupting the BBB for enhanced chemotherapy delivery. Most recently, promising results were reported from a preliminary study using a bradykinin analogue, labridimil (Cereport) children with brain tumors to disrupt the BBB prior to administration of carboplatin.[97] Convection-enhanced delivery is another new method of delivering tumor-targeted large molecule toxins directly into tumor through a surgically-placed catheter. Adult phase I trials using this methodology are currently underway to deliver recombinant chimeric proteins, such as interleukin-4, linked with a pseudomonas exotoxin. The tumor-targeted toxins are then taken up by glioma cells, causing cytotoxicity after internalization.[98]

Increased knowledge of the tumor biology and molecular traits of high-grade gliomas, just as with PNET tumors, points the way to their use as potential targets for therapy. One of the most common molecular alterations so far identified in high-grade gliomas involves the epidermal growth factor receptor (EGFR). Overexpression of EGFR is very common in pediatric high grade gliomas,[15] although gene amplification, the most common abnormality in adult, so-called "de novo" (primary) glioblastomas, is rarely seen in high-grade gliomas in children. Amplification of the platelet-derived growth factor alpha receptor (PDGFaR) gene and signaling by the PDGFaR/RAS/MAP tyrosine kinase pathway have been demonstrated in adult glioblastoma and play a role in the tumorigenesis of some pediatric medulloblastoma. This molecular pathway appears not to be as important for most pediatric high-grade gliomas, although PDGFR gene amplification was found in one of 14 high-grade gliomas in a recent study.[99] The phosphatidylinositol-3 kinase (PI3K)/ras/AKT pathway and downstream target, mammalian target of rapamycin (mTOR), mediates functions of cell survival and migration, for which the PTEN (phosphatase and tensin homology) gene is an important regulator. Mutations of the PTEN gene have been identified in 6% of pediatric malignant gliomas and 20% of glioblastomas.[100] Alterations in the p53 gene are fairly common in pediatric high-grade gliomas. Mutations of p53 were found in 40% of malignant gliomas in children > 3 years, similar to the rate seen in the tumors of young adults. However, overexpression of the p53 protein, found on one third of a series of uniformly-treated pediatric malignant gliomas, did not correlate with the presence of a mutation but did correlate with a poor prognosis.[14]

Small molecule inhibitors of several of these targets have been developed and are in early clinical trials for adult high-grade gliomas, including Iressa (gefitinib), targeting the EGF receptor tyrosine kinase,[13] Gleevec (imatinib), targeting the PDGF receptor tyrosine kinase,[21] and Sirolimus (rapamycin) and Everolimus (rapamycin derivative), targeting the PTEN oncogene-activated PI3K/ras/AKT/mTOR pathway.[13] Phase I trials of Iressa and Gleevec are ongoing for recurrent and newly diagnosed high-grade gliomas in children. Just as with

TABLE 1. *Common Pediatric Brain Tumors*

Tumor	Diagnosis	Stage/Grade	Surgery	Radiation Therapy	Chemotherapy (CHT)	Prognosis
PNET/Medulloblastoma	Brain MRI Histology	Staging: post-op brain MRI pre or post-op spine MRI CSF cytology No Grading (currently)	Radical resection improves prognosis	CSRT + primary site boost	Some form of adjuvant CHT indicated	
Medulloblastoma			Radical resection improves			
Average-Risk		No Metastases (M0) < 1.5 cm^2 residual	prognosis	Reduced-dose CSRT (24 Gy)	Platinum-based adjuvant CHT	80% 5-yr PFS
High-Risk		+ Metastases (≥M1+) or > 1.5 cm^2 residual		Standard-dose CSRT (36 Gy)	Platinum-based adjuvant CHT +/− radiosensitizer CHT during RT	60-80% 5-yr PFS
Infant (≤3 yrs)		+/− M0 or M1+ +/− residual >1.5 cm2		Defer RT	Platinum-based multiagent CHT	30-60% 5-yr PFS
Supratentorial PNET		+/− M0 or M1+ +/− residual >1.5 cm2	Radical resection improves prognosis	Standard-dose CSRT (36 Gy) + primary site boost	Platinum-based adjuvant CHT +/− radiosensitizer CHT during RT	50-60% 5-yr PFS
Glioma/Astrocytoma		No Staging (unless symptoms)				
Low-Grade Glioma						
Cerebellum	Brain MRI Histology	Grade: Pilocytic Astrocytoma (most)	Radical resection frequently curative	Rarely required	Rarely required	>90% 5-yr PFS
Supratentorial midline OPHG	Brain MRI No Histology (not routine)	Grade: Presumed Pilocytic or Low- Grade Astrocytoma	Rarely resectable	Conformal RT for prog dz (older child)	CHT to defer RT in younger children (carboplatin/VCR or PCV-TG)	40-80% 4-yr PFS
Cerebral	Brain MRI Histology	Grade: Pilocytic Astocytoma, Low-grade Astrocytoma, Mixed Glioma, or Other	Radical resection may be curative	+/− Conformal RT for residual/prog. dz (older children)	Rarely indicated	80% 5-yr PFS
High-Grade Glioma						
Brainstem/Pontine	Brain MRI No Histology (rarely)	Grade: Presumed Anaplastic Astrocytoma or GBM	Not resectable	Conformal RT (rarely curative)	Radiosensitizer CHT during RT (investigational)	≤ 5% 5-yr PFS
Cerebral	Brain MRI Histology	Grade: Anaplastic Astrocytoma or GBM	Radical resection improves prognosis	Conformal RT improves prognosis	Adjuvant CHT may improve prognosis	0-45% 5-yr PFS

CHT = chemotherapy; GTR = gross total resection; OPHG = optic pathway/hypothalamic glioma; RT = radiation therapy; CSRT = craniospinal radiation therapy; M0 = no metastases; PCV-TG = procarbazine/CCNU/vincristine-thioguanine; GBM = glioblastoma multiforme; M1+ = metastases(brain/spine/CSF cytology); PFS = progression-free survival.

the anti-angiogenic agents, it seems likely that these drugs will not be as effective as single agents, and in future studies they will probably be combined with other small molecule inhibitors, chemotherapeutic or anti-angiogenic agents to assess their additive or synergistic potential.

SUMMARY

Important factors that have combined to improve the long term survival of children with brain tumors include advances in neuroimaging, histopathology, neurosurgery, and radiation therapy technologies, coupled with the application of conventional chemotherapy. MRI, MR spectroscopy, and diffusion-weighted MRI have contributed to the success. Neurosurgical treatment is facilitated by functional MRI, intra-operative image-guided stereotactic techniques and electrophysiological monitoring. The use of 3-D conformal RT, intensity-modulated RT, stereotactic radiosurgery and radiosensitizing agents have increased the efficacy and safety of RT. Chemotherapy regimens, administered either alone or combined with RT have improved the survival and quality-of-life of children with medulloblastoma/PNETs, high-grade and low grade gliomas. The improved outcome of children with brain tumors is, undoubtedly, also due to their treatment on collaborative national or multinational studies; this remains absolutely essential for progress to continue. Important new therapeutic approaches include refinement of drug delivery strategies, analysis of prognostic biologic markers to stratify patients for optimal therapy, and to exploit unique properties of tumor cells to target drug delivery. The thrust of such approaches is especially directed at reducing the toxicity of therapy and improving quality-of-life and increasing disease-free survival.

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