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Supratentorial High-Grade Astrocytoma and Diffuse Brainstem Glioma: Two Challenges for the Pediatric Oncologist

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the known genetic alterations associated with pediatric supratentorial high-grade astrocytomas and diffuse brainstem gliomas.
2. Discuss the clinical and biologic prognostic factors for children with supratentorial high-grade astrocytomas and diffuse brainstem gliomas.
3. Explain the roles played by surgery, radiation therapy, and chemotherapy in the treatment of children with supratentorial high-grade astrocytomas and diffuse brainstem gliomas.

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ABSTRACT

Pediatric high-grade gliomas represent a heterogeneous group of tumors that accounts for 15%-20% of all pediatric central nervous system tumors. These neoplasms predominantly involve the supratentorial hemispheres or the pons, in which case the tumors are usually called diffuse brainstem gliomas. The diagnosis of supratentorial neoplasms is dependent on their histologic appearance. The maximum possible surgical resection is always attempted since the degree of surgical resection is the main prognostic factor for these patients. Older children (>3 years) with supratentorial neoplasms undergo a multimodality treatment comprised of surgical resection, radiation therapy, and chemotherapy. The addition of chemotherapy seems to improve the survival of a subset of these children, particularly those with glioblastoma multiforme. However, 2-year survival rates remain poor for children with supratentorial neoplasms, ranging from 10%-30%.

The diagnosis of a diffuse brainstem glioma is based upon typical imaging, dispensing with the need for surgery in the majority of cases. Radiation therapy is the mainstay of treatment for children with diffuse brainstem gliomas. The role of chemotherapy for these children is not clear, and it is, in general, employed in the context of an investigational study. Less than 10% of children with diffuse brainstem gliomas survive 2 years.

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Because the outcome for patients with either type of tumor is poor when standard multimodality therapy is used, these children are ideal candidates for innovative treatment approaches. ***The Oncologist*** *2004;9:197-206*

Introduction

High-grade gliomas are one of the most formidable challenges faced by pediatric oncologists who care for children with primary central nervous system (CNS) neoplasms.

Pediatric high-grade gliomas include a heterogeneous group of tumors with different sites of origin and histologic aspects, and they affect children of different ages. These tumors can originate from any site in the CNS, particularly the supratentorial region and the brainstem. They rarely originate from the spinal cord or the cerebellum. When arising from the brainstem, these high-grade gliomas are usually called diffuse brainstem gliomas. Histologically, most of these neoplasms contain only an astrocytic component and are called either anaplastic astrocytoma (AA; World Health Organization [WHO] grade III) or glioblastoma multiforme (GBM; WHO grade IV), depending on their grade. Tumors with mixed or nonastrocytic phenotypes are uncommon in pediatric patients.

The number of children with high-grade gliomas is much smaller than the number of adults with these neoplasms. Whereas 40%-50% of all pediatric CNS tumors are gliomas, supratentorial high-grade astrocytomas constitute only 6%-12% of all primary pediatric brain tumors, and diffuse brainstem gliomas constitute only 3%-9% [1].

The Central Brain Tumor Registry of the U.S. (CBTRUS) compiles the incidence rates of primary brain tumors originating from 14 state cancer registries. According to the CBTRUS, from 1995-1999, the overall incidence of high-grade gliomas among patients aged less than 19 years was 0.63 per 100,000 person-years. This incidence was almost equally divided between the sexes and among children of different ages. Supratentorial high-grade astrocytomas composed roughly one-third of all pediatric high-grade gliomas and demonstrated a striking difference in age-specific incidence, ranging from 0.05 per 100,000 person-years in children aged 0-4 years to 0.19 per 100,000 person-years in adolescents aged 15-19 years. The incidence of diffuse brainstem glioma was 0.18 per 100,000 person-years and the median age of affected children was between 6 and 7 years.

Despite an aggressive treatment approach, the outcome for children with these tumors remains poor; long-term survival rates range from <10% to 30% for most supratentorial tumors and are <10% for diffuse brainstem gliomas.

This review focuses on tumor biology and therapy for supratentorial high-grade astrocytomas and diffuse brainstem gliomas.

Supratentorial High-Grade Astrocytoma

At diagnosis, children with supratentorial high-grade astrocytomas display signs and symptoms attributable to the local brain area involved, including seizures, usually accompanied by signs and symptoms of increased intracranial pressure. Figure 1 shows a typical magnetic resonance imaging (MRI) scan.

Known Genetic and Molecular Alterations

Limited information is available on the mechanisms underlying the formation of pediatric supratentorial high-grade astrocytomas. Some of the genetic and molecular alterations described in pediatric neoplasms more closely resemble those

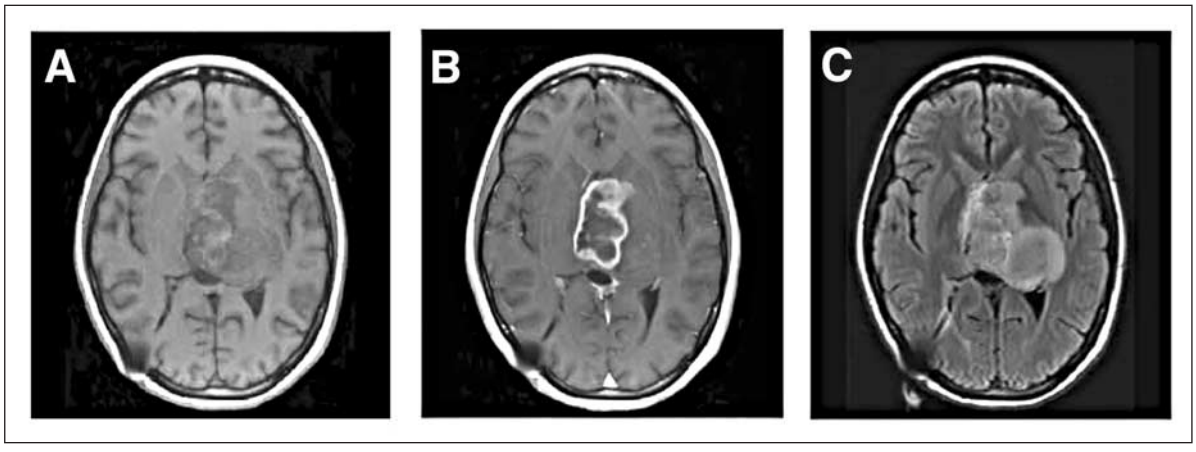

Figure 1. MRI scans of a patient with left thalamic GBM. *A and B) T1-weighted axial views without and with contrast. C) Axial fluid-attenuated inversion recovery (FLAIR) image.*

found in tumors of adults younger than 45 years (secondary GBM) than those found in tumors of older patients (primary GBM). However, other evidence, including other genetic differences between pediatric high-grade astrocytomas and adult secondary GBMs and the rarity of anaplastic progression from lower grade lesions in pediatric tumors, suggests that, despite the findings of some mutual genetic abnormalities in both groups, the mechanisms of tumorigenesis in children are distinct from those of similar neoplasms in adults. A recent study using comparative genomic hybridization of pediatric tumors corroborates this hypothesis [2].

With the goal of simplification, we divide the known genetic abnormalities implicated in tumorigenesis according to the affected pathway: the epidermal growth factor ligand and receptor pathway, the p53 pathway, the retinoblastoma tumor-suppressor pathway, the phosphatidylinositol 3′ kinase (PI3K) pathway, and the DNA repair pathway (methylguanine methyltransferase [MGMT] and mismatch repair [MMR]). Figure 2 depicts the known molecular pathways affected in pediatric high-grade astrocytomas.

Overexpression of epidermal growth factor receptor (EGFR) protein is common in pediatric supratentorial high-grade astrocytomas (up to 85% of cases), but gene amplification is rare, even when the protein is overexpressed [3, 4]. In contrast, *EGFR* amplification is the most common genetic abnormality observed in adult high-grade gliomas, particularly primary GBMs (40%-50% of all adult GBMs) [5]. Recently, RNA expression analysis of a small number of pediatric high-grade astrocytomas demonstrated overexpression of *EGFR* and other downstream genes associated with angiogenesis [6].

Abnormalities in the p53 pathway are common in pediatric supratentorial high-grade astrocytomas [4, 7]. Overexpression of the p53 protein is used as a surrogate marker of an alteration in p53 functional status and is not always associated with a *TP53* mutation. Overexpression of the p53 protein is found in one-third of patients. Overexpression of the MDM2 protein, which downregulates p53 transcriptional activity, is found in two-thirds of these patients. Overexpression of the p53 protein increases with tumor grade: one-fourth of analyzed AAs and half of GBMs overexpressed this protein. One-third of patients exhibit *TP53* mutations, and half these patients exhibit overexpression of the protein [7]. Among children with supratentorial high-grade astrocytomas, *TP53* mutations and protein overexpression are less prevalent in children younger than 4 years of age than they are in those older than 4 years of age [8]. Young children with supratentorial high-grade astrocytomas often undergo maximal surgical resection and chemotherapy, but do not receive radiation therapy (RT)

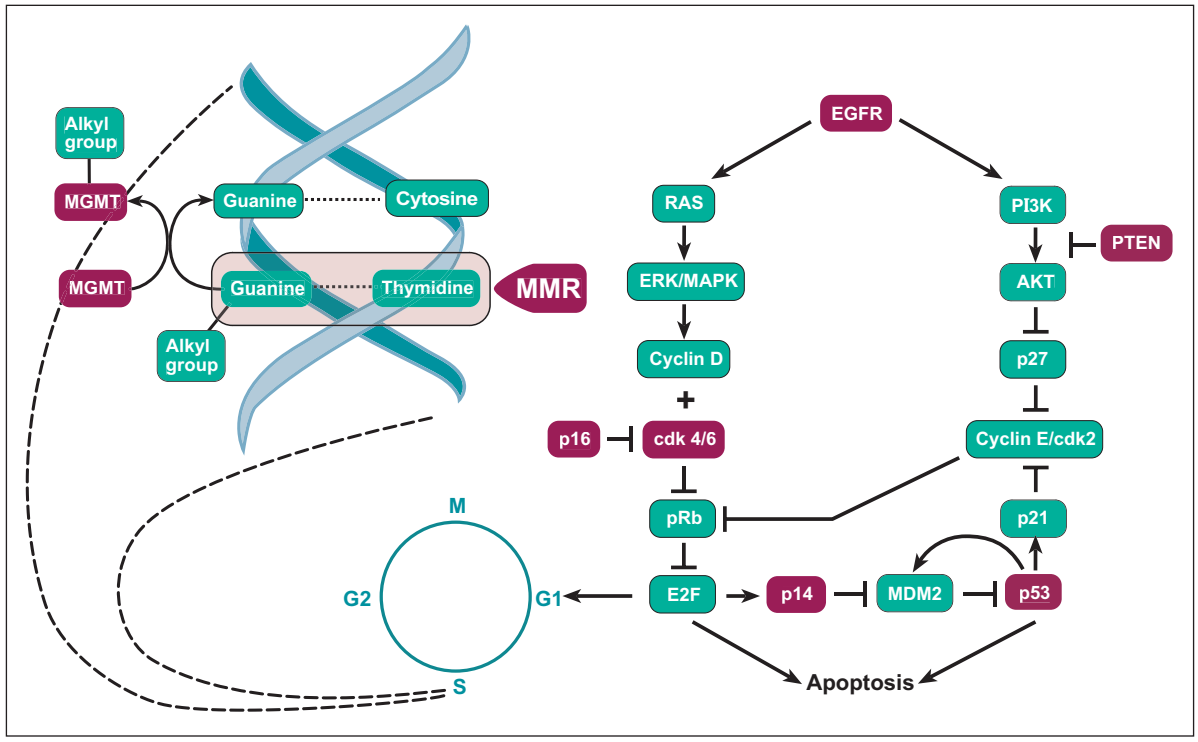

Figure 2. Abnormal intracellular pathways associated with pediatric high-grade astrocytoma and the interactions of these pathways. *Red boxes denote steps known to be affected in these neoplasms. Arrows indicate stimulation, and perpendicular lines indicate inhibition. The left side of the figure shows the activity of MGMT in removing alkyl groups from the O^6-guanine position and the activity of the DNA MMR system in removing abnormal stretches of DNA. Abbreviations: cdk = cyclin-dependent kinase; pRb = protein retinoblastoma.*

unless there is tumor recurrence or progression [9, 10]. Still, their 3-year event-free survival (EFS) rate ranges between 31% and 43% with this approach. It has been suggested that the absence of *TP53* mutations or protein overexpression in young children with high-grade astrocytomas could explain their better prognosis [8].

Disruption of the retinoblastoma tumor-suppressor pathway is observed in most adult high-grade gliomas, but less information is available about pediatric tumors [11]. Homozygous deletions leading to p16 inactivation occur in 50%-70% of adult tumors, but in only 9% of pediatric tumors [12]. *CDK4* amplification occurs in 15% and 6% of adult and pediatric tumors, respectively.

The PI3K pathway is involved in several important cellular functions including growth control, survival, and migration. The *PTEN* gene (phosphatase and tensin homology) serves as an important regulator of the PI3K pathway. *PTEN* mutations have been detected in 6% of pediatric AAs and in 20% of pediatric GBMs [12].

The MMR enzymes serve as a secondary proofreading system for DNA replication errors. Microsatellite instability, a surrogate marker of MMR deficiency, is rarely exhibited by adult gliomas but is found in 27% of sporadic pediatric high-grade astrocytomas (AAs or GBMs) [13]. The documentation of microsatellite instability in a small percentage of adults aged less than 45 years with sporadic gliomas supports the belief that pediatric patients and young adults may share some mechanisms of tumorigenesis [14].

MGMT removes methylating adducts from the O^6-guanine position. Studies evaluating paired samples of brain tumors and normal brain tissue taken from adults with high-grade gliomas found that nearly 60% of the neoplastic samples demonstrated a higher MGMT activity [15]. Similar studies involving smaller numbers of children with high-grade astrocytomas have demonstrated the same phenomenon, suggesting a role for MGMT in tumor formation [16].

Our knowledge of the genetic abnormalities found in pediatric high-grade astrocytomas is important for understanding the genesis of these neoplasms and may serve as a foundation for new therapeutic approaches for these tumors. Some of the disrupted pathways previously described are believed to be central to the formation of pediatric high-grade astrocytomas since they have been shown to be important mechanisms of gliomagenesis in laboratory and clinical studies [11, 17].

The outcome for children with supratentorial high-grade astrocytomas is poor with current therapeutic strategies. As we discuss later, a shift in treatment paradigm is taking place with the goal of specifically targeting some of these genetic abnormalities felt to be central to the formation of pediatric high-grade astrocytomas.

Known Prognostic Factors

The degree of surgical resection is the most important clinical prognostic factor for children with supratentorial high-grade astrocytomas, independent of other factors, such as tumor location, histologic grade, and age [18-20]. Patients undergoing complete or near-complete resection (resection of more than 90% of the tumor) fare better than those for whom a lesser degree of tumor debulking is achieved. The prognosis also seems to be better for patients with AAs than for those with GBMs [18, 20, 21].

Little information is available on the role played by biological markers in pediatric supratentorial high-grade astrocytomas. Five retrospective studies of pediatric patients have evaluated possible correlations between treatment outcome and the biological characteristics of the tumor. In a phase III study combining surgical resection, RT, and two randomly assigned chemotherapeutic approaches, *Pollack et al*. demonstrated that patients with tumors that overexpressed the p53 protein or exhibited a high proliferation index had less favorable outcomes than patients whose tumors did not exhibit these characteristics [7, 22]. A statistically nonsignificant negative association was found between the presence of a *TP53* mutation and survival. Another study, analyzing the expression of DNA topoisomerase IIα, a marker of cell turnover, confirmed the association between tumor proliferative activity and prognosis [23]. *Raffel et al*. demonstrated an association between a *PTEN* mutation and unfavorable outcome for patients with AAs and GBMs [12]. Finally, one institutional study involving 27 children with high-grade astrocytomas demonstrated an association between the overexpression of basic fibroblast growth factor protein and a lower rate of progression-free survival [24]. The basic fibroblast growth factor protein is a potent mitogen for both glial and endothelial cells and could be associated with malignant progression and growth of these neoplasms.

Treatment and Outcome

A recognition of the pattern of tumor spread is essential for an understanding of the importance of local control of supratentorial high-grade astrocytomas. These neoplasms are locally invasive and rarely have undergone leptomeningeal spread at the time of diagnosis (around 10% of cases) [19]. At recurrence, two-thirds of the failures are local only, 10% are isolated leptomeningeal failures, and the remainder are a combination of both [19].

Key factors involved in interpreting information about treatment outcome for pediatric patients with supratentorial high-grade astrocytomas are recognition of the complexity involved in classifying these tumors and the importance of central pathological review [25]. It is sometimes notoriously difficult to differentiate high-grade astrocytomas

from low-grade astrocytomas. In addition, variation in the histologic diagnosis is often dependent on the subjective interpretation of different neuropathologists [25].

Patients with Newly Diagnosed Disease

A multimodality treatment combining surgery, local RT, and chemotherapy is the standard approach for children older than 3 years newly diagnosed with supratentorial high-grade astrocytomas.

Surgery, the first step in therapy, has two main objectives: to obtain tissue for histologic diagnosis and to achieve a safe and maximal surgical resection. There is a strong correlation between primary tumor site and extent of resection [18]. Midline neoplasms are less amenable to radical resection (7% of tumors) than are tumors based in the cerebral cortex (56% of tumors).

The role of RT in the treatment of older children with high-grade astrocytomas is undisputed; all studies published during the past 25 years have used this treatment modality. It must be noted, however, that the techniques used in RT changed substantially during this period. In the first phase III pediatric study in which patients were randomly assigned to receive either local RT alone or local RT with weekly vincristine, followed by 1 year of carmustine, vincristine, and prednisone therapy, half the patients were treated with whole-brain RT, and cobalt-60 was still utilized [21]. Currently, new advances, including conformal three-dimensional RT and stereotactic techniques, allow us to better restrict the effects of RT to the involved area while sparing normal surrounding brain tissue.

Despite the absence of solid evidence to support its use, chemotherapy is routinely used to treat children with supratentorial high-grade astrocytomas. Forty patients with GBMs and 18 with AAs were treated in the study described above [21]. The 5-year EFS rates were 18% for the RT only group and 46% for those receiving chemotherapy. That study demonstrated a statistically significant better outcome for patients with GBMs treated in the chemotherapy arm (5-year EFS of 42%) than for those treated with RT only (5-year EFS of 6%). The number of patients with AAs was too small to show any meaningful difference in outcome.

Only one other large phase III study and a few phase II studies have tested the activities and efficacies of a variety of chemotherapeutic regimens in the neoadjuvant and adjuvant settings. With the exception of one retrospective analysis that demonstrated a superior outcome for children who underwent radical resection and received neoadjuvant chemotherapy [20], the studies reported equivalent results for both therapeutic strategies [18, 19].

In the largest phase III study, *Finlay et al.* randomly assigned 172 children who had undergone surgical resection to treatment with either RT and the chemotherapy regimen described above (standard) [21] or a combination of local RT and eight chemotherapeutic agents (8-in-1; vincristine, carmustine, procarbazine, cytarabine, hydroxyurea, cisplatin, dacarbazine, and methylprednisolone) given before and after RT [18]. The 5-year EFS rates were 26% for the patients receiving standard therapy and 33% for the group receiving the 8-in-1 regimen ($p > 0.52$).

Information about the outcomes of children younger than 3 years with supratentorial high-grade astrocytomas is scanty because the number of affected patients is very small. Two of the largest studies in this population were conducted by cooperative groups in North America, and both used maximal surgical resection followed by combination chemotherapy for 1-2 years [9, 10]. The first study treated the infants with 10 cycles of 8-in-1 chemotherapy; the second used cyclophosphamide and vincristine alternated with cisplatin and etoposide. RT was not consistently used after chemotherapy: it was often omitted altogether or used only to treat recurrent tumors. The overall 3-year EFS rate for the first study was 31% and for the second study was 43%.

Relapsed or Progressive Disease

The prognosis for children with recurrent supratentorial high-grade astrocytomas is poor. Tumors recurring locally in noneloquent areas are amenable to radical surgical re-resection. Conventional external-beam RT remains a treatment option for patients not previously treated with RT, particularly infants. Stereotactic techniques have been used to treat recurrent high-grade gliomas in adults, but their role in achieving local control for pediatric patients is unclear [26].

Quite often, chemotherapy is the only modality available for treating recurrent disease. Unfortunately, the activity of chemotherapeutic agents against recurrent pediatric high-grade astrocytomas is transitory and modest (objective radiologic responses are achieved in only 10%-20% of patients) [27].

Temozolomide, a new oral methylating agent, has shown promising activity and is well tolerated in adults with relapsed AAs [28]. In a pediatric phase II study using temozolomide in high-grade gliomas, 55 children with recurrent or progressive high-grade gliomas ($n = 34$) and diffuse brainstem gliomas ($n = 21$) were treated with temozolomide at doses of 200 mg/m^2 on five consecutive days [29]. The majority of children in the high-grade glioma group had supratentorial high-grade astrocytomas. The toxicity profile was similar to that found in adults, with a predominance of hematologic toxicity. Objective radiologic responses were seen in 12% of children with high-grade gliomas and in only 6% of those in the brainstem glioma

group. Another study included six children less than 18 years of age among a group of patients with newly diagnosed incompletely resected supratentorial high-grade astrocytomas who received upfront temozolomide as described previously [30]. One child with a GBM achieved a complete response to temozolomide, and two patients each with GBMs and AAs had a stable disease.

A small and select subgroup of pediatric patients with recurrent disease can be successfully treated with high-dose chemotherapy followed by autologous stem cell rescue [31, 32]. *Finlay et al*. used the combination of thiotepa and etoposide as consolidation therapy for 17 patients with high-grade astrocytomas [31]. Only one patient had not previously received RT, and two had not received chemotherapy. Five patients (29%), all of whom had no or minimal evidence of disease before treatment with high-dose chemotherapy, were long-term survivors, whereas no children with bulky disease survived. In a follow-up study, young children with recurrent high-grade astrocytomas were treated with consolidation therapy using thiotepa and etoposide with or without carboplatin ($n = 4$), or with a three-drug regimen using carmustine instead of etoposide ($n = 1$) [32]. All patients had not previously received RT, and four had minimal evidence of disease before consolidation therapy began. Three patients were long-term survivors, and only one of them had bulky disease before undergoing high-dose chemotherapy. These findings suggest that patients with minimal or no evidence of disease before treatment consolidation are most likely to benefit from the use of high-dose chemotherapy. Future studies should strictly target this ideal population.

Diffuse Brainstem Glioma

Patients with diffuse brainstem gliomas generally present with a short history (<6 months) of pyramidal deficits, cranial nerve involvement, and cerebellar signs and symptoms. A typical brain MRI shows an intrinsic, pontine-based infiltrative lesion that exerts significant mass effects on adjacent structures, including the basilar artery and the fourth ventricle (Fig. 3). The diagnosis is generally made based upon a typical aspect on the MRI, precluding the need for histological confirmation [33].

Known Genetic and Molecular Alterations

Because histologic confirmation is not necessary for diagnosis, genetic abnormalities have been described in only 65 pediatric patients with diffuse brainstem gliomas [4, 34-38]. Half the patients exhibited *TP53* mutations and, in one study, half the patients with these mutations also exhibited loss of the other p53 allele [34]. A recent study analyzing 28 brainstem gliomas demonstrated a correlation between WHO tumor grade and EGFR protein expression [38]. While 2 of 12 grade II tumors had detectable protein expression levels, seven of nine grade III and all grade IV tumors had EGFR protein detected. *EGFR* gene amplification was observed in only a minority of these neoplasms, particularly in grade III and IV tumors [38]. *PTEN* mutation was detected in only one tumor analyzed, and approximately 50% of all cases in one series demonstrated allelic loss in the long arm of chromosome 10 [34, 37].

Known Prognostic Factors

The two main clinical prognostic factors identified for children with diffuse brainstem gliomas are time between the onset of symptoms and diagnosis and presence or absence of florid neurologic deficits resulting from brainstem involvement [39]. Unfortunately, children with these tumors almost always have a short history at presentation

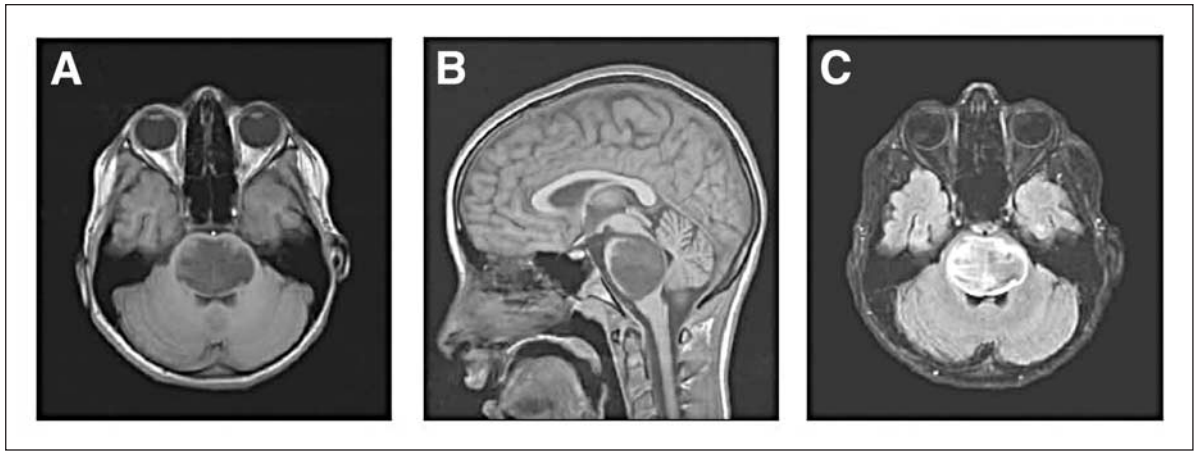

Figure 3. Typical appearance of MRI scans of a patient with diffuse brainstem glioma. *A and B) T1-weighted axial and sagittal images without contrast. C) Axial fluid-attenuated inversion recovery (FLAIR) image.*

Table 1. Summary of clinical studies for patients with diffuse brainstem glioma published in the past 5 years

Study/year	*n* of patients	Type of study	RT (Gy)	Chemotherapy	Median survival (months)	Survival
Allen et al. (1999) [45]	34	Phase I/II	HF 72	CBDCA twice a week along with RT	12	NA
Broniscer et al. (2000) [46]	29	Phase II	CF 54 (median)	Tamoxifen during and after RT	10	37% (1 year)
Bouffet et al. (2000) [47]	35	Phase II	CF 54-55 (median)	High-dose chemotherapy after RT with busulfan + thiotepa	10	<10% (2 years)
Doz et al. (2002) [48]	38	Phase II	CF 54	CBDCA prior to and along with RT	11	5% (2 years)
Wolff et al. (2002) [49]	20	Phase II	CF 54	Trophosphamide + VP16	8	0% (5 years)
Jennings et al. (2002) [50]	63	Phase II	HF 72	CBDCA/VP16/VCR prior to RT versus CDDP/cyclo/VP16/VCR prior to RT	NA	<10% (3 years)
Sanghavi et al. (2003) [51]	17	Phase I	CF 59.4	Topotecan daily along with RT	15	53% (1 year)
Marcus et al. (2003) [52]	18	Phase I	HF 63	Etanidazole along with RT	8.5 months	NA

Abbreviations: CBDCA = carboplatin; CDDP = cisplatin; CF = conventionally fractionated; cyclo = cyclophosphamide; HF = hyperfractionated; NA = not applicable; VCR = vincristine; VP16 = etoposide.

and display multiple neurologic deficits, and their outcomes are uniformly poor. In contrast, the outcome is often better for patients with neurofibromatosis type 1 and diffuse brainstem gliomas that would otherwise be considered typical according to clinical and radiologic criteria, even when no treatment is given [40]. Therefore, these brainstem abnormalities are considered a distinct clinical entity when they are associated with neurofibromatosis type 1.

Treatment and Outcome

Surgical resection is not recommended for patients with diffuse brainstem gliomas because of the high morbidity and mortality rates associated with any degree of resection of intrinsic brainstem tumors. Typical MRI findings are diagnostic, precluding the need for histologic confirmation [33].

RT is the mainstay of treatment, and conventionally fractionated local RT produces temporary neurologic improvement in at least 70%-80% of patients. Nevertheless, the long-term survival rate is dismal. Several studies using hyperfractionated RT have attempted to escalate the RT dosage, but the long-term survival rate remained around 10% [41]. In one of those studies, the RT dose was escalated to 78 Gy, but the 3-year survival rate was only 11% [42]. In that study, half the patients required steroids for longer periods after the end of RT, and nine patients (14%) developed intralesional cystic/necrotic changes, which are believed to be associated with the higher RT dose. In the largest phase III study of diffuse brainstem glioma, 130 patients aged 3-21 years were randomly assigned to treatment with either 54 Gy of conventionally fractionated RT (arm 1) or 70.2 Gy of hyperfractionated RT (arm 2), along with three courses of cisplatin delivered by continuous infusion [43]. For patients in arm 1, the 2-year survival rate was 7.1% and the median survival time was 8.5 months; for those in arm 2, the 2-year survival rate was 6.7% and the median survival time was 8 months.

In a pilot study, 32 children with diffuse brainstem gliomas received escalating doses of β-interferon during and up to 6 weeks after the end of hyperfractionated RT at a dose of 72 Gy [44]. Therapy was well tolerated, although a subset of patients experienced dose-limiting hepatic, hematologic, and neurologic toxicities. The long-term survival rate for those patients remained less than 10%.

Various chemotherapeutic approaches, including high-dose chemotherapy, have been tested for patients with newly diagnosed tumors, but the long-term survival rate remains dismal. A summary of some recent studies is shown in Table 1 [45-52].

New Therapeutic Approaches for Patients with Supratentorial High-Grade Astrocytomas and Diffuse Brainstem Gliomas

Patients with diffuse brainstem gliomas or supratentorial high-grade astrocytomas are good candidates for innovative experimental therapies because of their poor prognoses, combined with a lack of effective treatment. A substantial amount of basic and clinical research has focused on therapeutically targeting specific pathways important in the tumorigenesis of these neoplasms and on enhancing drug delivery to the site of these tumors by bypassing the blood-brain barrier. Clinical pediatric trials using small molecules that inhibit specific targets in

Table 2. Summary of new treatment approaches for children with supratentorial high-grade astrocytomas and diffuse brainstem gliomas

	Mechanism of action	Type of study
Biologic agents		
Imatinib mesylate	Platelet-derived growth factor receptor inhibitor	Phase I/II—newly diagnosed BSG and recurrent HGA
Gefitinib	EGFR inhibitor	Phase I/II—newly diagnosed BSG and incompletely resected HGA
O^6-benzylguanine	MGMT inhibitor	Phase I (along with temozolomide)—recurrent brain tumors
Tipifarnib	Farnesyltransferase inhibitor	Phase II—recurrent BSG and HGA
Gadolinium texaphyrin	Radiosensitizer	Phase I—newly diagnosed BSG
Improved drug delivery		
IL13-PE38QQR (Human interleukin-13 associated with Pseudomonas exotoxin A)	Intratumoral delivery of toxin via continuous convection-enhanced infusion	Phase I/II—recurrent HGA
Gliadel and O^6-benzylguanine	BCNU wafers in the surgical activity + MGMT inhibitor	Phase I—recurrent HGA

Abbreviations: BCNU = carmustine; BSG = brainstem glioma; HGA = high-grade astrocytoma.

activated cellular pathways (e.g., the EGFR pathway) are either under way or being developed. A summary of some of these new therapeutic strategies is shown in Table 2.

Conclusions

Despite recent advances in diagnostic techniques and in therapies used to treat pediatric brain tumors, little progress has been made in increasing the survival rates of children with supratentorial high-grade astrocytomas and diffuse brainstem gliomas. Therefore, a renewed effort has focused on new paradigms of treatment, particularly those that target the very specific mechanisms that confer a growth advantage to the neoplastic cells and those that optimize drug delivery to these tumors.

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