15 Pediatric Glioblastoma

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Abstract: Glioblastoma in children, when compared with adults, is relatively rare. Despite this rarity, it is apparent from the limited number of publications that pediatric glioblastoma is quite distinct from their adult counterparts. The differences pertain to the molecular genetics, effectiveness of the adjuvant therapies, and possibly the prognosis after treatment. With a plethora of path-breaking translational research coming through in recent times, a host of new information is now available on pediatric glioblastomas that holds great promise as far as the future treatment options are concerned. This chapter is an attempt to highlight the key clinical aspects of pediatric glioblastoma in the light of the emerging clinical and laboratory evidence.

Key words: High-grade glioma; Neuroimaging; Pediatric glioblastoma; Radiotherapy; Supratentorial

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Introduction

Glioblastoma (GBM) is the commonest and the most lethal primary brain tumor in adults (1). In contrast, GBM accounts for no more than 3–15% of primary central nervous system (CNS) tumors in children (2–7). This is despite the fact that CNS tumors are the most common solid tumors of childhood, and 40–50% of these tumors are constituted by the astrocytomas (8). Naturally, this relative rarity has been a great hurdle in properly deciphering the enigma of pediatric glioblastomas (p-GBM). Nevertheless, GBM remains an equally devastating disease in children with substantial morbidity and mortality. The reported median survival in p-GBM ranges from 13 to 73 months with a 5-year survival of less than 20% (2, 4, 6, 9–13). A few reports, however, reveal a relatively better prognosis and long-term survival figures in p-GBM as compared with adults (4, 9–11).

Maximal safe tumor resection followed by concurrent and adjuvant chemoradiation using oral temozolomide (TMZ) is the current standard of care in adult GBM (12). In fact, no such standard exists in children although a similar management policy is employed by most neurosurgeons across the globe. While there is sufficient evidence for the prognostic impact of maximal surgical excision of the visible tumor mass (4, 9, 10, 14), the concerns of irradiation on the developing brain and contradictory results of various chemotherapy regimens in p-GBM make the treatment decisions rather complicated and difficult in children.

A number of key clinical and laboratory investigations have led to a far better understanding of tumor biology of p-GBM today. Unlike in the past, these tumors are now considered to be distinctly different biological diseases compared with the adults. Numerous novel targeted drug therapies are emerging for the postoperative management of these tumors and hold great promise in times to come. However, it has to be agreed that the translation of the laboratory research into clinical patient management and patient outcomes have been relatively disappointing.

Epidemiology

Tumors of the CNS are the second most common childhood tumors after leukemia and are the commonest solid tumors in childhood (15). The overall incidence of primary CNS tumors in childhood is estimated to be approximately 30 per million (16). While astrocytic tumors account for 40–50% of the CNS tumors in children, high-grade gliomas are relatively rare. Estimation of the true incidence of p-GBM is often hampered by the fact that most studies tend to analyze GBMs (WHO grade IV) and anaplastic astrocytomas (WHO grade III) together, probably to derive a larger sample size for analysis. There is also a lack of consensus regarding the definition of pediatric age group. While the majority of studies consider 18 years as the cutoff, some studies consider 16 years or even 21 years for the same. On the contrary, many researchers also include adolescents in their analysis, thereby adding a lot of heterogeneity in the literature that hampers their holistic analysis.

As per the Central Brain Tumor Registry of the United States (CBTRUS) 2012 data, the incidence of pediatric high-grade glioma is approximately 0.85 per

100,000 (17). Most studies estimate the incidence of pediatric high-grade gliomas to be between 8 and 12% (18, 19). When only the GBM is considered, its incidence in the pediatric age group varies from 3 to 15% (2–7).

p-GBMs are most commonly reported in the second decade of life although their occurrence have been reported even *in utero* (2, 4, 5, 9, 20, 21). The highest incidence of p-GBM is seen between ages 15 and 19. This probably reflects the cumulative effects of different genetic insults in the eventual tumorigenesis. As far as gender predilection is concerned, most studies point towards a male predilection, the reasons for which are rather unknown. While it is unclear whether the patients' gender has any effect on the disease outcome, GBM in very young patients (<5 years) may have a slightly better prognosis compared to the older children.

As far as location is concerned, p-GBM is most commonly seen in the supratentorial brain, when the brainstem is excluded (12, 15, 20). Primary spinal cord high-grade gliomas constitute only 3% of the pediatric high-grade gliomas (22). In the supratentorial compartment, cerebral hemispheres are affected in nearly 50% of the cases. The incidence of deeper midline structure involvement, for example, thalamus, corpus callosum, hypothalamus, etc., is fortunately low (4, 23). In the infratentorial compartment, cerebellum is an extremely uncommon site with 1–2% of the GBMs in children affecting this site (24). Brainstem high-grade gliomas constitute nearly 20% of the intrinsic tumors in this area (25). Interestingly, when the nonbrainstem high-grade gliomas are analyzed, younger children are particularly susceptible compared with the older children and adolescents (26).

p-GBM remains a multifactorial disease similar to the malignancies at other age groups and systems. Prior history of ionizing radiations, particularly for hematologic malignancies like leukemia, is a proven factor in tumorigenesis (27, 28). Certain syndromes like Neurofibromatosis-1, Li-Fraumeni syndrome (characterized by inactivation of the tumor suppressor gene p53), and Turcot syndrome are also known to be associated with high-grade gliomas in children (23). We studied the association of matrix metalloproteinase (MMP)-1 gene of 110 patients with adult GBM and found a very high prevalence of 2G allele in these patients. A very strong association between 2G/2G genotype and GBM was detected in our study which indicated likely susceptibility for GBM in patients harboring this particular variant of MMP-1 (29). We also noted, in a separate study, that MMP-2 gene was not responsible for an increased susceptibility to high-grade gliomas in our population, unlike MMP-1 (30). These factors are discussed in detail below. However, it has to be agreed that the genetic syndromes constitute only a minuscule part of the entire spectrum of pediatric high-grade gliomas, the majority of which are sporadic without any clearly known predisposition. A number of genetic factors are now known to be associated with GBM in general and p-GBM in particular. These include p53 mutation, PDGFR mutation, H3K27M, etc., to name a few.

Pathology and Molecular Biology

GROSS AND MICROSCOPIC FEATURES

GBMs originate from the astrocytes, the chief glial constituent of the CNS. The gross and microscopic features of p-GBM are no different from the adults (5).

They are diffusely infiltrative despite their often apparent well-demarcated nature on imaging or even at surgery. These are usually dusky red or yellowish pink, friable, and vascularized tumors. Presence of thrombosed vessels inside the tumor mass is very much characteristic. There may be foci of hemorrhage or necrosis inside the lesion. Calcific components are rare but can be seen particularly in secondary GBMs. The usual sites of affections are supratentorial cerebral lobes like the frontal/temporal lobe. As mentioned before, deeper midline location, infratentorial compartment, and spinal cord locations are relatively uncommon (12, 15, 20). Although extracranial distant metastasis is rare, secondary dissemination inside the brain or the leptomeninges does occur in nearly 17% of patients (31).

Microscopically, these tumors are typically characterized by four histopathological hallmarks, namely, hypercellularity, nuclear atypia, pseudopalisading necrosis, and vascular endothelial cell proliferation. Multinucleated cells, bizarre nuclei, and neovascularization with glomeruloid formation are often detected. There are abundant mitotic figures with a high MIB labeling index, indicating a highly aggressive growth potential of the tumor. Satellite lesions are frequently seen. In one of the studies from our center, nearly 11% of GBMs were found to be multiple, the majority of the patients in that study being adults. Although these figures may not necessarily apply in pediatric population, our study showed that a high mitotic index (>40%), satellitosis, and a higher proportion of small cells correlate with tumor multiplicity in GBM (32).

PATHOLOGICAL VARIANTS/PATTERNS

WHO recognizes three variants of GBMs: giant-cell GBM, gliosarcoma, and, most recently, the epithelioid GBM. While the former two variants are relatively rare in children, epithelioid GBM, characterized by large eosinophilic cells, prominent melanoma-like nuclei, and often rhabdoid cells, is more common in children. These tumors tend to occur in the midline and are typically characterized by positive immunoreactivity for BRAF V600E, indicating their origin from a pre-existing low-grade precursor (33). GBM with primitive neuroectodermal components, small-cell GBM, and granular cell GBM are not true variants but specific patterns recognized by WHO. While the former is associated with a high risk of CSF spread, the latter two patterns portend poor outcomes despite the lack of necrosis inside the tumor (33).

MOLECULAR BIOLOGY

Incorporating the latest evidence emanating from laboratory research all over the world, WHO has updated its classification of brain tumors in 2016 (33). GBM is now classified as per the Isocitrate Dehydrogenase (IDH) gene mutation status. As a result, GBM can be either IDH mutation positive or IDH wild type. While the former group represents the secondary GBMs, the latter represents *de novo* lesions occurring mostly in elderly patients. But studies on pediatric high-grade gliomas, including GBMs, have noted a very low incidence of IDH mutation, particularly in younger children (34). Thus, for all practical purposes, p-GBM is almost always IDH wild type, although as Pollack et al. showed, the incidence of secondary GBM

(IDH mutated) may be higher in adolescents and younger adults (35). Lack of IDH mutation negatively impacts the outcome to therapy.

As far as the underlying genetic alterations are concerned, it is now well-known that p-GBMs have a higher incidence of p53 mutation/overexpression than mutation of epithelial growth factor receptor (EGFR) or deletion of phosphatase and tensin homologue (PTEN), the signatures of adult GBM. P53 mutation is particularly common in young children (<3 years). Interestingly, there may be overexpression of p53 in p-GBM even in the face of absent TP53 mutation (5, 36). Although, traditionally it was believed that PTEN mutation (with inactivation of its tumor suppressive effect on the downstream AKT pathway) played little role in p-GBM, certain recent studies have questioned the traditional belief and have noted activation of the AKT pathway, a feature that may negatively affect the patient outcomes (37). ATRX mutations have been reported in a fraction of p-GBMs, usually in the presence of p-53 mutation. Such tumors affect older children and are usually associated with better prognosis (38).

Recent studies have identified histone mutations (H3.3) in the DNA of pediatric high-grade glioma patients (39, 40). In fact, the H3K27M variant, wherein lysine is replaced by methionine at 27 positions, has been identified as an exclusive finding in pediatric high-grade gliomas. In addition, in slightly older children, replacement of glycine by valine or arginine at amino acid 34 of the H3.3 nucleic acid (G34V/R) is also frequently identified. While H3K27M variant is associated with poor prognosis, the outcome in patients with G34V/R is thought to be relatively better. Hemizygous deletions of ODZ3 have been described in the epithelioid variant of p-GBM. This particular variant, as already stated, shows BRAF V600E mutation, indicating its origin from low-grade pilomyxoid astrocytomas.

Vascular endothelial growth factor (VEGF) is commonly expressed by adult GBM cells. It is responsible for increased vascularity, tumor progression, and infiltration capacity of GBMs. As a result, anti-VEGF (bevacizumab) therapy is frequently employed in adult GBMs. The expression of VEGF is, however, relatively low in p-GBM, and it may be responsible for comparative ineffectiveness of anti-VEGF therapy in children (41). Somatic mutations of *PDGFRA* have also been recently reported in pediatric HGGs. This is in contrast to EGFRA mutations seen in adults. This has prompted anti-PDGFRA therapy in the form of receptor tyrosine kinase inhibitor imatinib (42, 43).

Apart from these clearly defined molecular aberrations, the pediatric HGGs seem to possess a significantly higher incidence of gains at 1q and losses at 16q and 4q. The 1p19q co-deletions are characteristic of oligodendroglial lineage. Some GBMs, particularly the secondary GBM, may have partial deletion of either 1p or more commonly 19q arms, and this may potentially confer a better prognosis (44). These GBMs are rare and were previously classified as GBM with oligodendroglial component (2007, WHO). As far as the O6-Methylguanine-DNA Methyltransferase (MGMT) promoter methylation status is concerned, it assumes an important prognostic significance in GBMs. Inactivation of MGMT generally correlates with chemoresponsiveness of these tumors. Studies on the expression of MGMT in p-GBM have revealed little difference in the promoter methylation status in children, with some studies noting even an overexpression of MGMT in tumors in children (45). It may be one of the reasons for reduced efficacy of TMZ in children compared with the adults. Whenever present,

the prognostic significance of the inactivating hypermethylation of MGMT confers a survival benefit to the affected children. Thus, a number of key molecular signatures of GBMs are now available for diagnosis and prognostication of high-grade gliomas in general.

Clinical Features

Symptoms of GBM are protean and are largely nonspecific. The duration of symptoms is usually short, often spanning a few months (2, 4, 20). The most common presentations are headache, vomiting, diplopia, and altered sensorium, indicating raised intracranial tension. It is reported as an initial symptom in 80–100% of patients (4, 20, 46). Children with GBM may present with acute neurological deterioration, usually from intratumoral hemorrhage, although an episode of seizure may also bring about such a dramatic presentation. The incidence of seizures as a clinical feature is estimated to be around 30%, being more common when frontotemporal lobes are affected or in the setting of secondary GBMs (4, 20, 46). Some authors have noted a relatively higher incidence of seizures in p-GBM, unlike in adults. Focal symptoms like neurological deficits, cranial nerve dysfunction, cerebellar symptoms, etc., depend on the location of the lesion. Neurological deficits, when present preoperatively, are known to affect postoperative prognosis negatively (47). Compared to the older children, infants and young children often present with nonspecific complaints, such as failure to thrive, lethargy, nausea/emesis, and macrocephaly, which, at times, can be difficult to diagnose. Assessment of the functional status is critically important in a disease like GBM. A number of scales are available to determine the functional status of children with brain tumors that are used preoperatively as well as during the posttreatment period. Karnofsky performance scale (KPS) is one such commonly utilized scale (4). A cutoff score of 80 generally differentiates good performance status from the poorly performing patients. In addition, neurological function scale (NFS) is another similar assessment tool in children (10). In our own study, the prognostic significance of preoperative performance status of these patients on the postoperative outcome was clearly demonstrated (4).

Neuroimaging

Neuroimaging plays an important part in the diagnosis, management, and prognostication of GBMs. Computed tomography (CT) and magnetic resonance imaging (MRI) form the backbones as far as the radiological assessment of these tumors is concerned. On CT and conventional sequences of MRI, these tumors appear as irregular, heterogeneously contrast-enhancing masses with significant perilesional edema. Although, some of the anaplastic astrocytomas may not enhance, GBMs almost always enhance. Necrosis, hemorrhage, and a garland pattern of enhancement are often characteristic of GBMs. The common differential diagnosis includes metastasis, lymphoma, brain abscess, etc. Although contrast-enhanced computed

tomogram is usually characteristic, MRI provides finer details needed for surgical as well as radiotherapy (RT) planning. Magnetic resonance spectroscopy typically displays choline peak with reduced N-acetyl aspartate in the region of the tumor although no such peaks may be seen in areas of necrosis. Diffusion-weighted images may show restricted diffusion with low apparent diffusion coefficient in the cellular parts of the tumor. While contrast images delineate the portions of the tumor with blood–brain barrier disruption, T2 fluid-attenuated inversion recovery (FLAIR) images clearly demonstrate the nonenhancing and edematous portions. Figure 1 shows the different radiological characteristics of GBM. Apart from the above diagnostic information, recent MRI techniques like functional MRI, tractography, etc., help in planning tumor resections, especially in eloquent locations. Perfusion-weighted MRI, although not routinely used, shows increased vascularity inside the tumor, a characteristic feature in high-grade gliomas. It can be performed by utilizing one of the three techniques, namely, magnetic resonance perfusion imaging, dynamic susceptibility contrast-MRI, and dynamic contrast-enhanced MRI (48).

An important role of neuroimaging is to assess response to therapy. Volumetric MRI is able to provide the extent of tumor excision, an important prognostic variable in GBMs. Moreover, the response assessment criteria like McDonald's criteria and RANO criteria rely on the posttreatment neuroimaging. In this regard, neuroimaging plays an important role in deciphering the true nature of two interesting radiological phenomena in high-grade gliomas, namely, "pseudoprogression" and "pseudoresponse" (48, 49). The former typically occurs after 3 months of chemoradiation when an erroneous observation of tumor progression is made when, in actuality, there is none. Different neuroimaging modalities

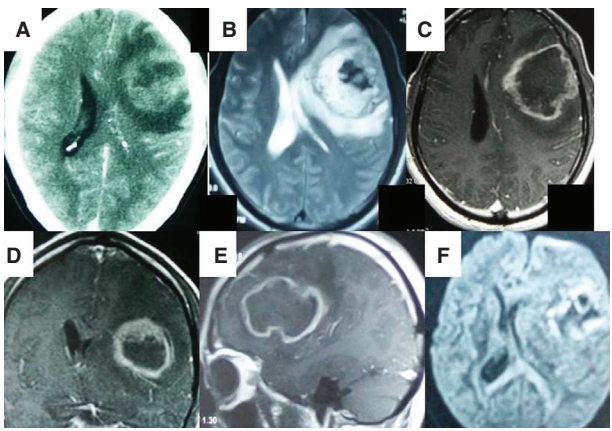

Figure 1 (A). Post-contrast computed tomography of the head shows a left frontal irregularly enhancing intraaxial mass of size approximately 4.5 × 4.5 cm with perilesional edema. The mass is causing effacement of the adjacent lateral ventricle. The mass is heterogeneously hyperintense on T2-weighted image with central necrosis **(B)**. The peritumoral edema and ventricular compression is well made out on T2 images (B). The mass shows peripheral and ring-like contrast enhancement **(C, D, E)**. The peripheral enhancing part shows hyperintensity on diffusion-weighted films suggestive of diffusion restriction **(F)**. (The image was taken in 3T MRI scanner, GE, USA.)

like MR spectroscopy, diffusion-weighted MRI, positron emission tomography (PET), and perfusion-weighted MRI, etc., usually reveal the true nature of this spurious radiological finding. In true tumor progression, the typical metabolite profile of elevated choline, choline: creatinine >2, and reduced N-acetyl aspartate peaks would be seen in MRS while there will be diffusion restriction on DWI. PET and perfusion-weighted MRI usually shows hypermetabolism and increased blood flow inside the enhancing area if there is true tumor progression, while the findings will be contradictory in pseudoprogression. Pseudo response, on the contrary, occurs as early as 24 h of anti-VEGF (Bevacizumab) therapy and is characterized by the lack of enhancement on contrast images even though the tumor is still there. Such pseudo responses are detected using T2 flair and diffusion-weighted MRI. While T2 flair shows the nonenhancing tumor as a hyperintense area, persistent diffusion restriction in the suspected area is usually diagnostic of residual tumor tissue. Neuroimaging has prognostic significance as well. In a recent study, Wangaryattawanich et al. (49) from MD Anderson Cancer Hospital showed that preoperative eloquent tumor location (P = 0.007), deep white matter invasion (P = 0.006), tumor volume (measured on contrast T1) >35,000 cm^3 (P = 0.08), and volume of nonenhancing tumor/brain edema volume (measured in T2 flair) >85,000 mm^3 (P = 0.003) were associated with poor survival in GBM.

Management

SURGERY

Maximal surgical resection followed by chemoradiotherapy remains the best current treatment in adult GBMs. Numerous studies have reiterated the utility of maximal tumor removal on both progression free as well as overall survival (OS) in p-GBM (4, 9, 10, 13, 14, 51). The Children's Cancer Group (CCG) study-945 showed that children with HGG who underwent a surgical resection of 90% or greater had a progression-free survival (PFS) of 35 ± 7% as compared with a 5-year PFS of 17 ± 4% in patients who did not (50, 51). Reporting on probably the largest single-center experience of p-GBM, we have also shown that the extent of tumor excision was a strong predictor of long progression-free survival as well as OS (4). The utility of maximal surgical excision has been proven in a recent multiple propensity analysis, the scientific value of which is as good as a randomized clinical trial (14). The extent of resection is, however, dependent on the location as well as extensions of the tumor (4). Brainstem location, midline supratentorial tumors, tumors affecting eloquent area, etc., are often difficult to excise completely without incurring significant neurological deficits. Apart from providing tissue for diagnosis, surgical debulking relieves tumor-related mass effect and potentiates the effect of the adjuvant therapy. Different intraoperative imaging techniques may allow larger extents of tumor excision which in turn translates into better survival outcomes. These advanced techniques include intraoperative neuronavigation, intraoperative ultrasound, intraoperative MRI, intraoperative cortical mapping, etc. Recent technological advances utilizing microfluidic chips allow for rapid analysis of the operative specimen for molecular signatures like IDH mutation within no time (51, 52). Therefore, it is possible now to make a molecular diagnosis

even intraoperatively. Such advances have the potential of facilitating intraoperative decision-making regarding the radicalism of the surgical excision in the future.

RADIATION THERAPY

Radiotherapy is an integral part of the comprehensive management basket of p-GBM. This is more so as the role of chemotherapy is not yet clear in these patients unlike their adult counterparts. Usually, the radiotherapy dose ranges from 50 to 60 Gy fractionated over 5–6 weeks (52, 53). Trials on hypo/hyper fractionation of the total dose have not shown any better results (54). It is routinely used in children aged more than 3 years. The primary reason why it should not be used before 3 years of age is that RT may lead to adverse neurocognitive complications due to its damaging effects on the developing brain. Moreover, it is believed that the tumors in the early years of life are rather indolent, responding less completely to irradiation (55, 56). The various long-term sequels of childhood cranial irradiation include endocrine dysfunctions, neurocognitive impairments, psychosocial and behavioral abnormalities, ototoxicity, growth abnormalities, and heightened chances of secondary malignancies (57). There has been a change in the way RT is administered in these patients. Previously, RT protocols encompassed the whole brain RT with additional boost at the site of the tumor with a 2-cm margin. However, with improvements in technology and accurate delineation of tumor margins, made possible by newer generation MRI scanners, currently RT is delivered using 3-dimensional conformal techniques. Thus, many of the earlier concerns with radiation treatment are no longer there. The conformal radiation treatment technologies include intensity-modulated RT, stereotactic RT, and proton beam RT (57). The latter techniques employ head fixation using rigid frames to enable precisely localized radiation. Therefore, recent advances have made RT in pediatric high-grade gliomas rather safe and effective.

CHEMOTHERAPY

Chemotherapy forms an important and integral part of the comprehensive treatment regime in adult GBMs. The same, however, cannot be said about the pediatric patients. Sposto et al. (CCG 943 trial) were the first to prove the effectiveness of chemotherapy (concomitant vincristine and adjuvant eight cycles of PCV regimen comprising procarbazine, CCNU, and vincristine) in high-grade gliomas (57). This regimen demonstrated a statistically significant improvement in the outcome of patients with GBM treated with chemotherapy compared with RT-alone group (5-year PFS: 42% vs. 18%). However, the regimen never reproduced similar results thereafter and hence failed to become a standard regime. It was later found that many of the patients included in that trial actually had low-grade gliomas. A subsequent trial looked at eight-drug chemotherapeutic regimen consisting of vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, prednisone, and dimethyl-triazenoimidazolecarboxamide (DTIC) in children younger than 2 years (50, 58). This trial did not show any benefit in p-GBM. Moreover, the regimen failed to show any effectiveness in older children as well. Intensive chemotherapy after surgical excision has shown promising results in children, provided the tumor excision was

complete. The treatment using HIT-GBM-C protocol showed 5-year OS rate for these patients, with total resections of 63% versus 17% for historical controls. The OS was 19% at 60 months from diagnosis (50, 59). Some trials have also looked into the high-dose chemotherapy with bone marrow rescue in p-GBM, but these trials are mainly applicable for recurrent cases and their results have not been consistently proven. Unacceptable drug toxicity is usually the major handicap in these trials (60).

The landmark trial by Stupp et al. showed that the addition of concomitant and adjuvant TMZ improved progression-free survival and OS in adult GBMs (12). Five years' OS in this study for the TMZ arm was 9.8% versus 1.9% for the radiation alone arm. This trial has established the current therapeutic standard of concurrent and adjuvant TMZ in adult GBM. The Stupp trial, however, did not include p-GBMs. Thus, despite its landmark findings, the Stupp trial has not really helped matters as far as the p-GBM are concerned. Most studies indicate that TMZ chemotherapy does not affect survival figures in children, although a recent study has shown otherwise. A trial similar to the Stupp trial involving the pediatric patients did not show any benefit of TMZ in children (61). MGMT promoter methylation, whenever present, potentiates the activity of TMZ even in children. Thus, the ambiguity of the results of these studies has put a question mark on the routine use of chemotherapy in p-GBM vis-à-vis adult GBM, at least as of now. The PCV regimen is still used at many centers, often as a salvage therapy after disease recurrence.

ANTIANGIOGENESIS INHIBITORS

p-GBMs express VEGF similar to the adults. The clinical trials with anti-VEGF therapy (bevacizumab), however, have been rather disappointing in children (62). In a study of 10 patients with supratentorial HGGs and two studies with diffuse intrinsic pontine glioma (DIPG), clinical responses to bevacizumab were inferior to those in adult patients (62). Trials of combining chemotherapeutic agent (irinotecan) with bevacizumab has not improved the outcome either (63). Thalidomide, another antiangiogenic agent, has also failed to prove its efficacy in clinical trials when combined with RT. In particular, this combination led to rather high and unacceptable toxicities (64).

MOLECULAR TARGETED THERAPY

Recent insights into the molecular biology of gliomas in general and pediatric high-grade glioma in particular have led to the development of a number of agents directed specifically against these molecular targets. These include monoclonal antibodies like imatinib (anti-PDGFR) (65); erlotinib; gefitinib (anti-EGFR) (66, 67); and tipifarnib, a farnesyltransferase inhibitor (68). Most of these agents are in Stage I/II trials and have not really lived up to the expectations. One of the primary reasons for lack of expected success could be the fact that a number of tumorigenic pathways act simultaneously in these tumors, thereby negating the effect of blockade of a particular pathway. Similar to the above agents, lobradimil, a bradykinin agonist, was tried with chemotherapy in a Phase II trial involving pediatric high-grade glioma, with a view to

enhance the drug permeability of the chemotherapeutic agents. The fate was unfortunately no different (68).

EMERGING NEWER DRUGS AND THERAPEUTIC MODALITIES

A number of other drugs and therapeutic modalities are being tested currently in the laboratories that hold great promise in the days to come. These include integrin inhibitors (cilengitide), EGFR inhibitors (cetuximab, nimotuzumab), novel antiangiogenic agents (enzastaurin, cediranib), histone deacetylase inhibitors (vorinostat, valproic acid), and dendritic cell vaccines. These agents have been tested in children with HGG and have shown good response in the clinical trials. Some agents are in the pre-trial recruitment phase and are likely to enter clinical trials in days to come. These include boron neutron capture therapy, cytomegalovirus-specific cytotoxic T cells, IL-13-PE38QR (an enzymatically active portion of pseudomonas exotoxin A conjugated with human interleukin-13), smoothened inhibitor LDE225, telomerase inhibitors, gamma secretase inhibitors, poly(ADP-ribose) polymerase inhibitor, etc., to name a few. Details of these advances are beyond the scope of this chapter and can be found in other articles (69).

Factors Affecting Outcome

The OS in p-GBM varies from 10 to 73 months (2, 4, 6, 9–12). Majority of the studies emphasize on improved survival figures in p-GBM compared with the adults (4, 9–11). There are studies on the long-term outcomes in p-GBM, defined as survival beyond 3 years of diagnosis. Although the factors determining the outcomes are still being studied, a number of factors are already known to predict survival in p-GBM in particular (Table 1). Of all the reported factors, the extent of surgical tumor excision probably remains the strongest predictor of outcome in p-GBM as of today.

TABLE 1 Factors Predicting a Longer Survival in p-GBM

Demographic factors	• Age <5 years of age • Female sex
Clinical factors	• Longer duration of symptoms • Presentation with seizures • Lack of preoperative neurological deficits • Good preoperative performance status
Radiologic factors	• Superficial, well-circumscribed tumor • Lack of extensive edema or intense contrast enhancement
Pathologic factors	• Lack of necrosis • Epithelioid/giant-cell variants • Low-MIB-1-labeling index

Table continued on following page

TABLE 1 Factors Predicting a Longer Survival in p-GBM (Continued)

Molecular genetics factors	• IDH mutation • MGMT promoter methylation • P53 over expression • PTEN deletion • Bcl underexpression • Expression of the tissue inhibitor of matrix mettaloproteinase-1 and coexpression of the extracellular matrix metalloproteinase inducer and matrix metalloproteinase–2 • Lack of self-renewal genes like HOXA9/HOXA10 • Presence of BRAF/ATRX/G34V/R mutations
Treatment-related factors	• Gross total tumor excision • Chemoradiotherapy • Completion of entire treatment regime

Conclusion

p-GBM is a rare but distinctly different biological disease compared with the adults. Specific sets of genetic aberrations characterize p-GBMs. In the absence of concrete evidence for adjuvant chemotherapy, maximal surgical excision followed by adjuvant RT (in children >3 years of age) remains the current best treatment strategy for these tumors. Prognosis in the majority of children is better than the adults which in turn may be explained by a different biological make up of these tumors. With rapid scientific advances being made in this field, newer targeted molecular and other treatment strategies are likely to emerge and change the future course as well as the prognosis of p-GBM.

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