Exploratory therapy for brainstem gliomas

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Abstract

Brainstem gliomas comprise both slow-growing and highly aggressive tumors, the latter carrying a dismal prognosis of approximately 10 months in children. Given their common locations along the brainstem, they are often not amenable to surgical resection. There are currently a host of exploratory therapies under investigation ranging from immunotherapy, small molecular inhibitors, epigenetic-modifying agents, and radiation protocols to combat these difficult-to-treat tumors. Recent discoveries highlighting the role of H3 histone mutations in diffuse midline glioma oncogenesis have yielded a variety of new targetable antigens and aberrant signaling pathways. Although many of these studies have shown promise in terms of inhibiting tumor growth and disease progression, results to date have been modest in their ability to translate into meaningful clinical benefit. This review will serve as an updated report on the current state of literature concerning pre-clinical and clinical therapies being investigated for brainstem glioma. In addition, this review will serve as a guide for clinicians as we review the evolving nomenclature of brainstem gliomas, commonly presenting symptoms, diagnostic tools, and standard therapies.

Keywords: brainstem glioma; diffuse midline glioma; diffuse intrinsic pontine glioma; H3K27M

Introduction

Brainstem gliomas are a heterogeneous group of tumors that arise along the brainstem. They are composed of both slow-growing and highly aggressive tumors, with the latter carrying a dismal prognosis of approximately 10 months in children. Due to their common locations along the brainstem, these tumors are often not amenable to surgical resection. There is a current unmet need to improve therapeutic options for patients with brainstem gliomas.

Evolving Nomenclature

Brainstem gliomas are traditionally classified into two main categories: Diffuse Intrinsic Pontine Gliomas (DIPGs) and Diffuse Midline Gliomas (DMGs). This dichotomy is based on the location of the tumor, with DIPGs arising in the brainstem and DMGs in the supratentorial region. However, recent discoveries have highlighted the importance of genetic and epigenetic factors in the development and progression of these tumors.

There has been an evolution in the nomenclature of brainstem gliomas, and it is important to understand the current terminology. For instance, the term “Diffuse Intrinsic Pontine Glioma” (DIPG) is now considered a histopathological diagnosis and is used when the tumor is restricted to the Pons. The term “Diffuse Midline Glioma” (DMG) encompasses tumors arising in the midline, including those in the brainstem and those in the supratentorial region such as the optic chiasm.

Current Understanding of Brainstem Gliomas

Brainstem gliomas are often classified into two main categories: low-grade and high-grade gliomas. Low-grade gliomas, such as pilocytic astrocytomas, are slow-growing and often diagnosed in children. High-grade gliomas, such as glioblastoma, are more aggressive and typically diagnosed in adults.

Genetic and Epigenetic Factors

Recent studies have highlighted the importance of genetic and epigenetic factors in the development and progression of brainstem gliomas. Mutations in the H3F3A gene, which encodes for the histone H3.3, are commonly found in DIPGs. This mutation results in the replacement of arginine with lysine at position 27 (H3K27M) and is associated with a poor prognosis.

Epigenetic modifications, such as DNA methylation and histone modifications, also play a crucial role in the development and proliferation of brainstem gliomas. These modifications alter the expression of genes and can lead to tumor cell proliferation.

Therapeutic Approaches

Despite advances in understanding the biology of brainstem gliomas, there remains a significant unmet need for improved therapeutic options. Current treatment options include surgical resection, radiation therapy, and chemotherapy. However, these approaches often result in limited clinical benefit.

Novel Therapeutic Strategies

Advances in immunotherapy, small molecular inhibitors, epigenetic-modifying agents, and radiation protocols have led to the development of novel therapeutic strategies. These strategies aim to target specific tumor antigens and aberrant signaling pathways.

Immunotherapy

Immunotherapy involves the use of immune-activated cells to target and destroy tumor cells. This approach has shown promise in brainstem gliomas, with studies demonstrating the feasibility of using adoptive cell transfer and checkpoint blockade.

Small Molecular Inhibitors

Small molecular inhibitors are designed to target specific tumor antigens and aberrant signaling pathways. These inhibitors can inhibit the activity of enzymes involved in tumor cell proliferation, survival, and migration.

Epigenetic Modifiers

Epigenetic modifiers, such as histone deacetylase inhibitors and DNA methyltransferase inhibitors, have shown promise in brainstem gliomas. These agents can interfere with the epigenetic modifications that lead to tumor cell proliferation.

Conclusions

Brainstem gliomas are a challenging disease to treat due to their slow-growing and aggressive nature. Advances in understanding the biology of these tumors have led to the development of novel therapeutic strategies. However, there remains a significant unmet need for improved treatment options. Further research is needed to identify new targets and develop effective therapies for brainstem gliomas.

Acknowledgments

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Abbreviations

BBB, blood-brain barrier; CNS, central nervous system; DMG, diffuse midline glioma; DIPG, diffuse intrinsic pontine glioma; MRI, magnetic resonance imaging; CT, computed tomography; WHO, World Health Organization; SVZ, subventricular zone; CSF, cerebrospinal fluid; TNC, tenascin-C; ncRNA, non-coding ribonucleic acid; XIST, X-inactive-specific transcript; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; TCR, T-cell receptor; CAR, chimeric antigen receptor; PD-1, programmed cell death protein 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; HDAC, histone deacetylase; PARP-1, Poly (ADP-ribose) polymerase 1; STAT3, Signal transducer and activator of transcription 3; PDGFRa, platelet-derived growth factor receptor alpha; ACVR1, Activin A receptor, type I; CDK, cyclin-dependent kinase; HTS, high-throughput sequencing; RT, radiation therapy; FUS, focused ultrasound; SDT, sonodynamic therapy; ALA, 5-aminolevulinic acid; CED, convection-enhanced delivery; DWI, diffusion weighted imaging; Gd, gadolinium enhanced T1-weighted imaging; MET, mesenchymal-epithelial transition; GSK-3, glycogen synthase kinase-3; GD2, disialoganglioside; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic lymphocyte-associated antigen 4; CMV, cytomegalovirus; S-ALA, S-aminolevulinic acid; Gp, Gamma ray; FACT, Facilitates chromatin transcription.

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Introduction

Brainstem gliomas are tumors of glial cell origin that arise in the midbrain, pons, or medulla [1]. The brainstem bridges the brain and spinal cord to relay messages to the body and regulates life-sustaining functions of the cardiovascular and respiratory systems. While nearly 20% of pediatric brain tumors arise in the brainstem, these tumors account for less than 2% of all gliomas in adults [2, 3]. The median age at the time of diagnosis is 7 years in children and 34 years in adults, corresponding to a bimodal distribution [3, 4]. Given their sensitive location, lesions that arise in the brainstem impose complex and unique challenges to diagnosis and surgical treatment. In addition, the tightly regulated blood-brain barrier (BBB) generally complicates the medical management of central nervous system (CNS) tumors. Due to the aforementioned reasons and the associated aggressiveness of these tumors, the median survival of pediatric patients is approximately 10 months [1]. With such a dismal prognosis and limited therapies available, brainstem gliomas represent a significant obstacle to the field and are the subject of intense research efforts. This review aims to highlight the pathophysiology, diagnostics, and emerging treatments of brainstem gliomas with a focus on diffuse midline gliomas (DMG), previously known as diffuse intrinsic pontine glioma (DIPG). Given the propensity of these lesions to arise in children and worse mortality when compared to adults, this review will focus on the literature regarding the pediatric population. However, we will present findings regarding adult brainstem gliomas when pertinent. Furthermore, adult brainstem gliomas more closely resemble other high-grade intracranial gliomas and are more likely to benefit directly from innovations and therapeutic regimens implemented for these aims. As such, their discussion is beyond the scope of this review.

Common symptoms of brainstem lesions

Patients with low-grade brainstem glioma may present with a long history of minor symptoms such as neck stiffness, torticollis, and headache [3, 5, 6]. Those with high-grade tumors may present more acutely with double vision, weakness, gait disorders, dysarthria, dysphagia, behavioral changes, nausea, and vomiting [3, 5–8]. Patients may also present with clinical signs of hydrocephalus, particularly for tumors in the periaqueductal region [3, 9]. During the physical examination, sixth and seventh cranial nerve impairments are commonly observed, as well as papilledema, and crossed deficits, which refer to contralateral facial and extremity signs and symptoms [3, 5, 6, 10].

Diagnostic imaging and utility of radiomics

The imaging modality of choice is magnetic resonance imaging (MRI) with and without contrast [11]. Computed tomography (CT) is not recommended because lesions in the brainstem tend to be isodense [12]. Focal brainstem gliomas on MRI tend to be small (< 2 cm), well-circumscribed, cystic, and non-infiltrating [11, 13, 14]. On the other hand, high-grade gliomas are typically expansile and represent an infiltrative process [11]. Also, they have low signal intensity on T1-weighted images and heterogeneous or hyperintense signals on T2-weighted images [11, 13, 14]. Uniform contrast enhancement can be seen in 40% of these patients [13, 14].

At present, radiomics is a dynamic and growing field whose application to brain tumors can help with differential diagnosis, tumor classification, identifying mutations, as well as predicting treatment response and recurrence [15, 16]. Nevertheless, there is scarce evidence regarding the use of radiomics in brainstem gliomas [17]. Due to recent advances in artificial intelligence, subtle features derived from imaging studies may be aggregated to understand better and predict disease progression and recurrence of brainstem gliomas.

Role of biopsy

Stereotactic lesion biopsy is recommended when the diagnosis is not possible with brain imaging alone [18]. To appropriately select patients who might benefit from target-directed therapies, a tissue sample of the lesion is required for molecular profiling. The role of stereotactic biopsies in brainstem gliomas has been controversial, particularly in the developing brainstem of pediatric patients. However, with improved MRI resolution and stereotactic technology, there has been some shift in the risk-to-benefit ratio. Hersh et al. conducted a retrospective study and examined outcomes in 58 patients who had undergone a biopsy for brainstem lesions [19]. They found persistent post-operative neurological deficits in 2 cases, a pseudo meningocele occurred in 1 patient, and 8 cases required an additional procedure for more tissue sampling, with a majority resulting without complication or need for re-biopsy. The authors concluded that given proper patient selection for procedures, biopsies could be advantageous and safe.

Tumor pathology and molecular classification

Brainstem gliomas have historically comprised three major types: diffuse or focal malignant brainstem gliomas, exophytic medullary gliomas, or tectal gliomas [20]. Due to advances in our understanding of the molecular underpinnings of these tumors, DMG H3K27M-mutant has been classified as a distinct subtype of malignant brainstem gliomas by the World Health Organization (WHO) [21]. Nearly 80% of DIPG tumors carry a somatic mutation in the gene that encodes histone H3 [22]. Patients with H3K27M-mutant tumors have worse overall survival [23]. H3K27M mutation lends itself to dysregulation of the epigenome and associated regulatory genes. Histone 3.1 and 3.3-specific K27 mutations are also associated with somatic gain or loss-of-function alterations, respectively, and these genetic aberrations can act synergistically with disrupted epigenetic mechanisms to promote tumorigenesis [24–27].

Diffuse midline glioma

The pons is the most commonly affected structure in DMG, extension along white matter tracts into the cerebellum or thalamus is a distinguishing feature in approximately half of all patients. Leptomeningeal dissemination, supratentorial, or spinal cord invasion occurs less frequently [25, 28–31]. Recently, attention has turned to the subventricular zone (SVZ), a stem cell niche in the postnatal brain, as a possible site of pathogenesis. Patterns of invasion along the SVZ corridor or intraventricular cerebral spinal fluid (CSF) seeding of the SVZ have been postulated as previously unappreciated mechanisms of spread that could explain the involvement of the SVZ and frontal horns of the lateral ventricles [31]. These tumors are thought to arise in the ventral pons, where a population of stem-like Olig2+ pontine precursor cells can be found. A distinct peak of pontine precursor cell proliferation coincides with the highest incidence period for DMG, between the ages of 6 and 7 years [32]. Postmortem, as well as MRI-based morphometric and histological analyses, support the hypothesis that DMGs originate from an Olig2+ neural precursor cell [32–34].

Exophytic medullary glioma

In contrast with diffuse brainstem gliomas, most exophytic medullary gliomas are low-grade tumors that arise dorsally from subependymal glial tissues [35]. Pilocytic astrocytomas (WHO grade I) comprise a large majority of these tumors, though grade II astrocytomas can also be appreciated. Despite their indolent disease course, tumor progression may occur into the fourth ventricle or the surrounding cisterns.

Tectal gliomas

Tectal gliomas present a distinct type of slow-growing adult brainstem glioma, of which only a small subset of tumors affects children [36]. Similar to dorsally exophytic gliomas, WHO grade I and II tumors are the predominant histologic type, although rare entities include high-grade astrocytoma, oligodendroglioma, ependymoma, ganglioglioma, medulloblastoma, primitive neuroectodermal tumor,
metastases, and other lesions. Tectal gliomas grow parallel to the periaqueductal gray matter and are sometimes referred to as “pencil gliomas,” due to their narrowed appearance on imaging [37]. The benign clinical and radiologic course of these tumors rarely necessitates intervention beyond CSF diversion, though chemotherapy may be considered in more aggressive lesions [38].

**Standard treatment**

The current standard treatment for brainstem glioma is based on conventional radiotherapy, chemotherapy, and rarely surgical resection [3, 39]. The choice between these therapies depends on whether the tumor is focal or diffuse [11]. Conventional radiotherapy represents the basis of most treatment protocols and should be used in any patient with progressive symptoms [11, 39, 40]. Response to this therapy depends on the location of the tumor and histologic type. In the case of a focal lesion, radiotherapy may be provided postoperatively to the residual tumor [41, 42]. In combination with radiotherapy, temozolomide may increase survival in adult patients [43].

**Role of surgical intervention**

DMG/DIPG is generally considered an inoperable disease due to its infiltrative nature and aggressive disease course. However, there has been a growing role for surgical resection of select focal lesions. Improved surgical technology and imaging modalities have enhanced the safety of resection of select brainstem lesions. Resection can be considered in benign tumors, tumors with clear margins, cystic tumors, dorsal tumors that protrude into the fourth ventricle, and tumors located at the cervicomedullary junction [41]. In the case of hydrocephalus as a result of tectal brainstem lesions, endoscopic third ventriculostomy can be considered and has been shown to be effective and safe [44, 45].

Overall, the optimal role of surgical resection in brainstem gliomas remains unclear for higher-grade lesions. In a single surgeon retrospective study, 77 pediatric patients who had resection for brainstem glioma were identified. At last follow-up, the authors reported a permanent neurologic deficit in 16 patients and a postoperative complication in 12 patients. This study reported an overall median survival of 26 and 8 months for Grade III and IV gliomas, respectively [46]. Other reports have demonstrated benefits with surgical resection of higher-grade lesions, but these studies are limited by their cohort heterogeneity and differences in selection criteria for surgery [47, 48].

**Emerging biomarkers**

Several biomarkers have been identified that may provide therapeutic benefit, although there is a need for more research about their utility [49]. One feasible biomarker is tenascin-C (TNC), whose overexpression correlates with aggressive behavior in DMG and may work as a disease biomarker and possible target for treatment [50]. Non-coding RNAs such as XIST and XIST-210, have shown potential in predicting survival [51]. Similarly, Liu et al. identified several long non-coding RNAs found to be differentially expressed in DIPG/DMG [52].

Recent studies use noninvasive biomarkers such as pons size, MRI perfusion and diffusion, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) to differentiate between disease progression and treatment changes [53]. For example, increasing pons size was found to be significantly associated with shorter survival [54]. The authors also concluded that pons measurements resulted in lower inter-reader variability compared to other image-based measurement techniques. In addition, mismatches between diffusion-weighted imaging and gadolinium-enhanced T1-weighted imaging correlate with a worse prognosis in DIPG/DMG [55]. MRS can be used to measure cell tumor-associated metabolites choline and N-acetyl aspartate, which can help differentiate between high and low-grade gliomas [56–58]. Interestingly, Panigrahi et al. showed that the myo-inositol/choline ratio, as measured by MRS was shown to correlate with overall survival following radiotherapy [59]. Emerging biomarkers are summarized in Table 1.

**Emerging therapies in brainstem glioma**

Preclinical and clinical studies for brainstem gliomas have historically been modeled after adult glioblastoma data for the development of therapies. Unfortunately, this has proven rather unsuccessful given that the biology of GBM and DIPG/DMG appears to be fundamentally distinct, requiring more tailored approaches. The advent of reliable preclinical models, increased availability of tumor tissue samples, and collaborations via international patient and sample registries have directly translated into several new preclinical discoveries and spurred a multitude of clinical trials. Currently, there are a total of 46 U.S.-based clinical trials in DMG, including both active (closed for enrollment) trials and trials open for recruitment, which are listed in Table 2.

**Adaptive lymphocyte transfer**

Adaptive lymphocyte transfer refers to vaccinating patients during a period of profound lymphodepletion following myeloablative or non-myeloablative chemotherapy (Figure 1). When infused with autologous T cells that are primed or “educated” ex vivo, this produces a dramatic T cell expansion in vivo. The discovery of the histone H3.3 driver mutations in DMG provided a plausible target for T-cell immunotherapy. A recent study by Chheda et al. demonstrated that the development of T-cell receptors (TCR) with an affinity for H3.3K27M peptide by CD8+ T-cells could efficiently identify and kill H3.3K27M-mutant glioma cells [60]. Transduced T cells displayed success in targeting this specific neoantigen, with limited off-target toxicity. In contrast, however, Immisch and colleagues concluded that this mutation was not a suitable target for immunotherapy in DMG [61], underpinning the difficulty in successful targeting of histone mutations and developing effective immunotherapies.

The disialoganglioside GD2 is a highly expressed cell surface antigen in patient-derived cell lines of H3K27M-mutant gliomas. As such, human GD2-targeting chimeric antigen receptor (CAR)-T cells are capable of specific, GD2-antigen dependent killing and cytokine production, with a demonstrable survival benefit in treated animals [62]. This data, along with evidence that GD2-CAR T cell therapy is well-tolerated in clinical trials of patients with neuroblastoma, has permitted this approach to proceed to a Phase 1 trial (NCT04196413) [63, 64].

Another CAR T cell-based trial (BrainChild-03, NCT04185038) opts for locoregional delivery of B7-H3-specific CAR T cells via an indwelling catheter directly into the tumor resection cavity or ventricular system. Though the precise function of the transmembrane B7-H3 protein is unclear, its overexpression in DMG, tumor specificity, and correlation with malignancy grade, support its use as a therapeutic target [65]. Preliminary results from the BrainChild-03 trial indicate that this outpatient CAR T cell therapy is feasible and well-tolerated [66].

**Immune checkpoint inhibitors**

Although immunotherapy has emerged as a formidable solution to brainstem gliomas, these tumors are capable of modulating the immune microenvironment to dampen the host immune response, limiting the efficacy of these interventions [67–69]. In response, the development of immune checkpoint blockade strategies (e.g. anti-PD-1, anti-CTLA4) has been at the forefront of combatting tumor-induced immunosuppression [70]. Immune checkpoint inhibitors have had limited applications in sporadic childhood cancers, likely as a result of low neoantigen expression. The only currently active trial of checkpoint inhibitor monotherapy with pembrolizumab (anti-PD-1) is enrolling patients with recurrent, progressive, or refractory DIPG following radiation therapy or chemotherapy (NCT02359565). For patients with newly diagnosed DIPG, a safety and feasibility trial of cemiplimab (anti-PD-1) in addition to standard radiation therapy is underway. Though the CD40...
## Table 1 List of emerging biomarkers for brainstem gliomas

<table>
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<tr>
<th>Class of Biomarker</th>
<th>Biomarkers identified</th>
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## Table 2 Summary of therapeutic strategies currently under investigation in US-based clinical trials (www.ClinicalTrials.gov, Accessed October 2022)

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Table 2 Summary of therapeutic strategies currently under investigation in US-based clinical trials (www.ClinicalTrials.gov, Accessed October 2022) (Continued)

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**Immu-no-metabolites**

An emerging facet of immunotherapeutic approaches currently in clinical trials explores immuno-metabolic targets as potential avenues for treatment. Indoleamine 2,3-oxidase-mediated immune suppression in the DIPG tumor microenvironment can potentially be reversed and may improve outcomes in patients who respond to conventional radiation and chemotherapy, which is currently the subject of a Phase 2 trial (NCT04049669) [72, 73]. Separately, specific inhibitors of polyamine synthesis and uptake by tumor cells have been developed to halt rapid cell proliferation in DIPG [74].

**Epigenetic-based therapies**

Exploratory therapies have emerged that alter the epigenome to inhibit disease progression [75]. In a study conducted by Grasso et al., 83 drugs were screened for the ability to limit cell viability in DIPG cell cultures. Histone deacetylase (HDAC) inhibitors such as panobinostat emerged as the most promising candidate to maximally decrease cell viability and expression of proliferation-related genes [76]. HDAC inhibitors inhibit enzymes that remove acetyl groups from histone proteins, thereby leading to a chromatin structure that is conducive to gene expression [77] (Figure 2). In a series of experiments reported by Borsuk and colleagues, HDAC inhibitors panobinostat and romidepsin were found to have a synergistic effect in killing DIPG cell lines when combined with imipramine [78]. Similarly, Eytan et al. showed decreased cell survival of H3K27M-mutant glioma cells treated with HDAC inhibitor vorinostat in combination with PARP-1 inhibitors [79]. While most studies have focused on HDAC inhibitors, James et al. found that the demethylase inhibitor, GSKJ4 showed benefit in DIPG by inhibiting glioma cell growth and colony formation in vitro [80]. Furthermore, they found that athymic mice had significantly less subcutaneous glioma cell growth following intraperitoneal injections of 100 mg/kg GSKJ4 for 10 consecutive days.

**Kinase inhibitors**

Kinase inhibitors are especially potent agents for targeting H3K27M-mutant DMG cells. STAT3, a key component of the JAK-STAT pathway, induces cancer cell survival and proliferation when upregulated [81]. In a xenograft mouse model, investigators found that treatment with a STAT3 pathway inhibitor (WP1066) decreased tumor growth and improved overall survival [82]. This study also concluded that treatment with this STAT3 inhibitor led to partial restoration of H3K27me3, a repressive mark that is commonly lost in H3K27M-mutant DIPG/DMGs. Furthermore, inhibition of platelet-derived growth factor receptor (PDGFR) alpha/beta has yielded some promising results [83]. In a recent case report of a single patient with H3K27M + /PDGFRα + DMG, the addition of anlotinib, a multi-targeting tyrosine kinase inhibitor temporarily halted disease progression on brain MRI [84].

ACVR1 is a gene that encodes the serine/threonine kinase ALK2 [85]. ALK2 is a bone morphogenic protein receptor and plays an important role in regulating many organ systems [86]. As such, it has emerged as a potential target for treating patients with H3K27M-mutant DMG. Carvalho et al. found that inhibition of ALK2 led to decreased proliferation and reduced cell viability of patient-derived ACVR1-mutant tumors orthotopically implanted in xenograft mice [85]. Despite improvement in survival, Carvalho et al. found that ALK2 inhibition did not result in a cure, and most ALK2 inhibitors tested provided only modest benefit. Interestingly, despite the ACVR1 gene mutation’s association with H3K27M-mutant gliomas, the presence of this mutated gene is thought to confer mildly improved survival. This presents a valuable avenue for further studies as it is not fully understood to what extent H3K27M-mutant gliomas are dependent on ACVR1 mutations for oncogenesis and proliferation.

**Small molecule inhibitors**

Previous studies have highlighted the role of G1/S cell cycle checkpoint dysfunction with H3.3K26M+ gliomas [87-89]. Sun et al. showed that treatment with the CDK 4/6 inhibitor, palbociclib, inhibited the growth of DIPG/DMG glioma cells in vitro [90]. Barton et al. also found that CDK4/6 inhibitors prolonged the survival of mice with brain stem gliomas [91]. More recently, the combination of the BBB-penetrant proteasomal inhibitor marizomib with panobinostat, identified via high-throughput screening (HTS), has resulted in a Phase 1 trial (NCT04314311) [92]. An advantage of HTS lies in the ability to screen drug candidates based on combined metrics such as cell cytotoxicity and CNS penetration, to maximize the translational potential of these strategies. Furthermore, this study design allows us to identify disease-specific mechanisms that underlie drug susceptibility and resistance.

**Radiation therapy**

Radiation therapy has been the mainstay of therapy in DMG, and its use continues to be a vital component of active clinical trials. Recent trials have aimed to delay disease progression while minimizing symptoms, toxicities, and time spent in the hospital [93]. Re-irradiation of brainstem gliomas is feasible, and its safe dosing and timing continue to be explored (NCT01469247). While hyperfractionated RT has been shown to have no role in the treatment of DMG, a hyperfractionated regimen of 15 Gy in three fractions for the palliative treatment is currently being compared to the standard 20 Gy dose, which is typically administered in ten fractions (NCT03841435) [94-97]. Many of the active clinical trials in DMG include RT in their treatment regimens, and as such, efficacy data of novel combination therapies should be interpreted within the context of RT’s well-known role in delaying DMG progression.

**Focused ultrasound and somodynamic therapy**

In addition to radiation therapy, focused ultrasound (FUS) with microbubble administration has provided another noninvasive strategy that aims to permeabilize the BBB to panobinostat, for example [98]. Alternatively, somodynamic therapy (SDT) exploits the local cytotoxic effects of convergent low-frequency ultrasound beams.
and non-toxic sono-sensitizing agents [99, 100]. One such therapy is SONALA-100, whose cytotoxic effect is mediated by 5-aminolevulinic acid (ALA), and its maximum tolerated dose is being investigated when used in concert with the MR-guided Exablate 4000 Type 2 device [101–103].

**Convection-enhanced delivery**

Convection-enhanced delivery (CED) leverages one or more stereotactically implanted catheters to directly infuse drugs into an area of interest under controlled pressure. The ability to fairly assess its efficacy in GBM and DMG has been limited due to several technical and physical hurdles, in addition to the variable mechanisms of action of candidate agents. The latest trial of MTX-100, a water-soluble panobinostat nanoparticle formulation, is compatible with CED and directly bypasses the BBB, which has been an important limitation of systemic forms of panobinostat (NCT04264143) [104]. CED’s mechanism of drug infusion via principles of bulk flow affords certain biophysical advantages over diffusion-based systems, namely its ability to deliver higher doses of therapeutic agents without the associated dose-dependent toxicities, as well as an increased range of tissue penetration [105–107].

**Conclusion**
Immunotherapy, small molecule inhibitors, cell cycle inhibitors, and radiation therapy are currently emerging as the most plausible approaches to improving patient outcomes in brainstem glioma given the limited benefits of surgical resection. New paradigms for treatment have also made their way to clinical trials and may very well represent the future of treatment in brainstem gliomas. Strategies range from oncolytic viruses to radioligands capable of delivering radiation at the cellular level. [108–110]. A more profound understanding of DMG biology has led to the identification of novel targets that play essential roles in chromatin remodeling, nuclear export, and sphingolipid/ceramide metabolism [111–113]. In addition, the impact of recently discovered H3K27M mutations in an overwhelming majority of DIPG continues to fuel research into epithigenome-modifying agents such as histone deacetylase inhibitors and other hypomyelinating agents. Likely, these emerging therapies will need to be administered in a combinatorial fashion to maximize progression-free survival. Furthermore, other exploratory therapies for intracranial gliomas may likely be repurposed to treat brainstem gliomas, namely in adults. The innovative nature of these bench-to-bedside efforts is evidence of the neuro-oncologic field’s commitment to altering the landscape of pediatric brainstem glioma therapy as we know it.

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