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REVIEW

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Diffuse intrinsic pontine gliomas in pediatric patients: management updates

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Abstract

Background This review explores how diffuse intrinsic pontine glioma (DIPG) diagnosis and treatment have evolved and are improving.

Main body Authors used various sources from 2000 to present time to compile information on diffuse intrinsic pontine glioma in the pediatric population. The following topics were included: diagnosis procedure, molecular analysis, stereotactic biopsy, radiation therapy and other treatments. Historically, diffuse intrinsic pontine glioma's anatomical proximity to crucial brain stem structures prevented biopsy thus limiting diagnostic and molecular analysis. However, with the optimistic rise of the stereotactic biopsy technique, identifying genetic and other biological markers for targeted treatments is more feasible. Previous investigations have identified a histone mutation that appears in 80% of DIPG cases and there is plenty of exploration into how to unravel the effects of the resulting chromatin modification. For example, new pharmaceuticals like Panobinostat and ONC201 show promise.

Conclusion Advances in stereotactic biopsy technology have resulted in more accurate diagnosis opening more avenues for molecular analysis and thus, targeted treatments. DIPG requires more exploration to improve outcomes for patients.

Keywords Pediatric glioma, Pontine, H3K27M, Biopsy, DIPG

Background

Introduction and overview

Diffuse intrinsic pontine glioma (DIPG) is a type of brain stem glial tumor found in the ventral pons [1]. DIPGs are a subset of high-grade gliomas (HGG), which account for as high as 20% of pediatric central nervous system tumors [2] and 10–15% of all pediatric tumors [3]. DIPGs are an astrocytoma that is categorized according to World Health Organization as grade II, III, or IV. As a high grade (WHO III or IV) glial neoplasm in the brain stem with an infiltrating and diffuse nature, DIPGs are inaccessible for surgical resection [4–6]. Impacting a median age of 6.5 years [1], DIPG displays a low survivability of 16–24 months post-treatment [5, 7] and greater than 90% of patients die within 2 years of diagnosis [3]. Additionally, when considering prevalence by sex, there is slightly higher incidence in males compared to females [8]. Theories about the etiology of this tumor correlate to the rapid rate of cerebral tissue development occurring in childhood. Pontine precursor cells in the ventral pons, found in the region where DIPG originates, have two generation peaks throughout the lifespan. The first peak is during infancy, while the second peak occurs during middle childhood, the same age range of median diagnosis of DIPG (6–7 years) [9] (Fig. 1).

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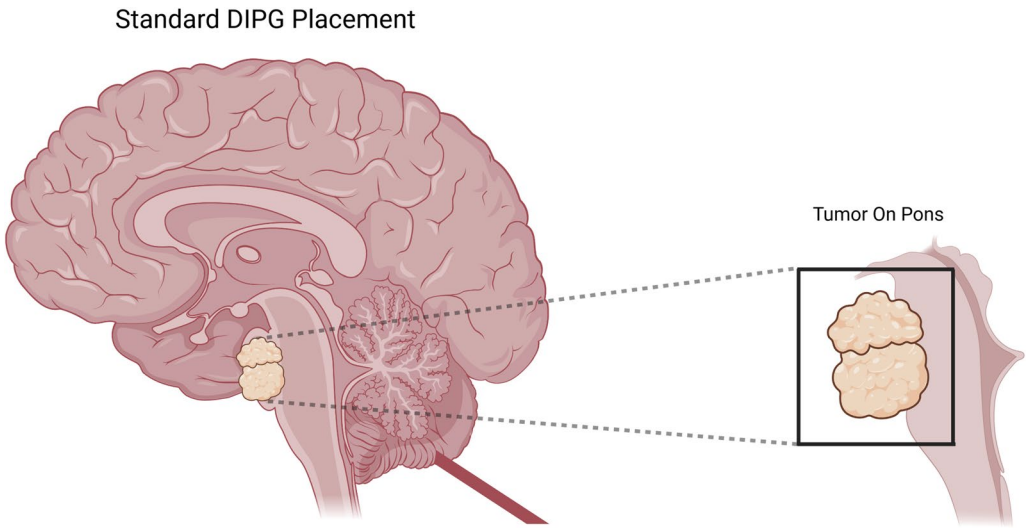

Fig. 1 The characteristic placement of diffuse intrinsic pontine gliomas is at the base of the brain in the pons, a structure that plays a vital role in controlling many essential bodily functions like heart rate and breathing [1, 3]. However, it is important to note that there is no standard position of this tumor as it is by nature, a diffusely infiltrated tumor

Main text

Diagnosis

Regarding diagnosis, 2 of the 3 brain stem dysfunctions (cranial nerve deficit, coordination dysfunction, and pyramidal tract affection) must be present and persist for 6 months. Furthermore, 50–66% of the pons must be infiltrated [3]. The infiltration capacity of DIGP leads to constriction and pressure on anatomical structures and white matter tracts adjacent and near to the ventral pons. Such compression generates various clinical presentations and symptoms of the disease. DIPG often affects cranial nerves VI and VII, which are responsible for eye movement and facial movement, respectively. Compression of these cranial nerves results in early symptoms of abducens palsy, disconjugate eye movement, and diplopia. Often, presentation of these symptoms occurs within a month of a child's diagnosis [10]. Further enlargement of the tumor leads to symptoms such as ataxia, dysmetria, dysarthria, Babinski sign, and loss of motor skills [10]. A small portion of pediatric patients (10%) develop hydrocephalus as a symptom [1]. Additional symptoms that insinuate a diagnosis may include < 10% of patients developing intracranial pressure and motor/muscular abnormalities (increased tone, hyperreflexia, clonus etc.) [11, 12]. Until very recently, the infiltrating nature of the tumor upon the brain stem rendered biopsies to be considered inadequately informative, and too risky for medical justification [13]. Likewise, most biological models of DIPGs were derived from autopsies [13]. Therefore, to verifiably diagnose a child suspected of DIPG, MRI (with and without contrast) demonstrates the greatest success. Radiographic features of DIPG include a T1-hypointense and T2-hyperintense tumor. Specifically, 50% of the pons' cross-sectional area must be involved [14]. Acquiring circulating tumor DNA through the cerebrospinal fluid (CSF) is a future endeavor to potentially aid in DIPG diagnosis [15]. Lastly, when considering genetics, 80% of DIPG cases have included a H3K27M mutation [16]. This mutation is characterized by a universal loss of H3K27 tri-methylation and subsequent acetylation which completely modifies the chromatin landscape [17]. Other investigated mutations potentially involved in DIPG include loss of FBXW7 in H3.3G34R/V and BCOR mutations in H3.1K27M [18].

Molecular analysis

The significant developments in molecular analysis of these DIPG tumor tissues have provided substantial evidence for distinguishing pediatric DIPGs from adult HGGs [19]. Specifically, pathognomonic mutations Lys27Met (K27M) and Gly34Arg/Val (G34R/V) in genes encoding histone H3.3 and H3.1 (H3F3A and HIST3H1B, respectively) have been identified in certain pediatric gliomas, allowing for the creation of a biologically and clinically distinct subcategorization of DIPGs [6]. 80% of DIPG cases exhibiting the H3K27M mutation require a reclassification as a diffuse midline glioma, H3K27M-mutant [15]. This molecular subgrouping is particularly compelling, as granular subtype classifications in other pediatric central nervous system (CNS) tumors have allowed for the exploration of tailored therapeutic approaches [15]. Information

on molecular phenotypes derived from the acquisition of actual malignant tissue (biopsy) can also provide researchers and physicians valuable insights into treatment and prognosis [19]. H3K27M mutations, due to the location of K27 in a critical site for post-translational histone modification, have severe impacts on gene transcription regulation and DNA methylation [3]. Patients with H3 mutations tend to exhibit a more aggressive clinical course and a worse response to radiation therapy [3]. Knowing the clinical implications of histone H3 mutation in DIPGs, molecular analysis can serve to critically advance our understanding of the mechanisms of diffuse midline glioma, H3 K27M-mutants [3]. Aside from the molecular composition of the tumors themselves, recent investigations into biomarkers of DIPGs suggest that neoplastic DIPG cells may release a variety of soluble molecules (i.e., nucleic acids and proteins) into the bloodstream [20]. Liquid biopsies, which require only minimally invasive techniques to analyze these biomarkers in blood and CSF may serve as a viable alternative to tissue biopsy [20]. Monitoring levels of potential biomarkers, such as microRNA (miRNA), could potentially allow for the collection of a more comprehensive clinical and molecular assessment of DIPGs. In a preliminary study, serum samples taken from DIPG patients at the time of MRI diagnosis showed a distinguishable miRNA profile thus demonstrating a potential new strategy for diagnosis [20] (Fig. 2).

Computerized tomography and magnetic resonance imaging

Traditionally, the diagnosis of DIPGs has been based solely on clinical assessments and neuroimaging findings (usually the appearance of an expanded/infiltrated pons and the encasement of the basilar artery) [15, 19]. MRI is the most common modality utilized; however, computed tomography (CT) may also prove informative in the diagnosis of DIPG [19]. 22 DIPG cases (in which tissue samples were available) were retroactively reviewed in 2019 and these findings confirmed the consistency of imaging techniques with the biological markers detected [21]. Despite these MR-affirming findings, related research suggests that modern imaging techniques are sufficiently reliable only in the cases of typical DIPG, whereas atypical presentations may require histological confirmation of the diagnosis [22]. Evaluations of consistency in MR imaging analysis interpretations revealed a significant amount of variation among pediatric neurosurgeons, especially in atypical tumor presentations [22]. The inconsistency in interpretations likewise led to differences in therapeutic approaches, therefore revealing a lack of standardization in diagnosis and management of DIPGs [22]. With the modernization of surgical techniques (i.e., stereotactic technology and operative microscopes) the concept of foregoing biopsies has been called into question [23]. Given the disadvantages of imaging techniques and the reduced operative risk of brain stem biopsies due to improved technology, [23] stereotactic biopsy must continue to be explored.

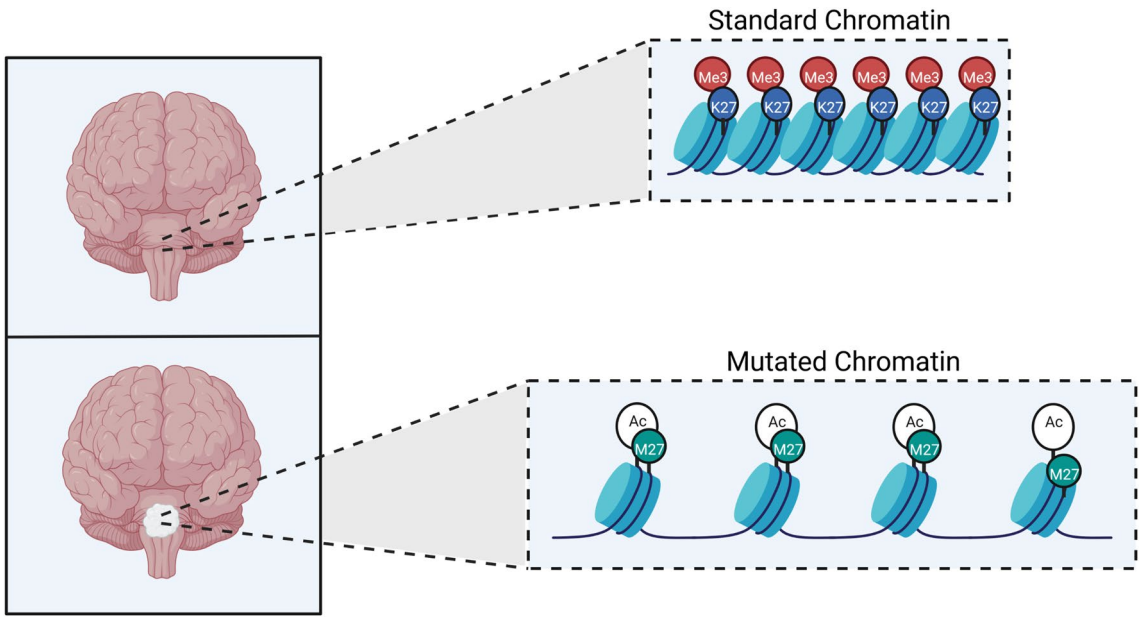

Fig. 2 The common histone mutation found in DIPG pediatric patients, H3K27M, is characterized by a loss of H3K27 tri-methylation and subsequent acetylation which opens the chromatin, promoting oncolytic activity in this site [15]

Stereotactic biopsy

Recent approaches to molecular analysis via stereotactic tumor biopsy have revealed distinct molecular characteristics of DIPGs in comparison with other high-grade astrocytoma (HGA) [6]. Developments in the ability to analyze DIPG tumor tissue greatly enhances overall understanding of the disease and increases the potential for new therapy development. Following a review of cases in neurological units, researchers concluded that stereotactic biopsies of DIPG could be incorporated in diagnostic protocols [24]. Traditionally, biopsies are approached through the trans-cerebellar route to obtain tissues from the area of highest yield, which typically lies within the T2 or T2 FLAIR hyper-intense region [5]. A burr hole is made, the dura is cauterized and opened, the pial surface is then cauterized, and the pre-set trajectory fixation guide is placed [5]. The core-biopsy needle is then inserted and tumoral tissue is obtained. Researchers have recently recommended offering stereotactic biopsy to all children with suspected DIPGs because of the improvements in the safety of brainstem biopsy [25]. Unlike other gliomas, treatment of DIPGs is solely dependent on identifying genetic markers for specifically targeted therapies [5]. Therefore, stereotactic biopsy is increasingly valuable as a diagnostic tool. Following tissue diagnosis, further work can be useful to identify the histone genetic mutations and methylation discrepancies in DIPGs [5]. Biopsy-derived tissue allows tumor sequencing for individualized treatment pathways. For example, in immune-based therapy trials, it is critical to identify targetable surface integers through biopsy-derived tissues [25] (Fig. 3).

Frameless robot-assisted stereotactic biopsy of DIPGs in pediatric populations serve to address complex cases and heavy workflow. As histological diagnosis was achieved in all cases, frameless robotic-assisted biopsy was evidently a safe, effective, and highly accurate procedure to achieve diagnosis for pediatric patients with DIPGs [27]. In one study, researchers had one group of patients with DIPGs undergo microsurgical biopsies, and another group of patients with DIPGs undergo frameless robot-assisted stereotactic biopsies [26]. It was found that operation time, postoperative ICU stay time, and postoperative hospitalization time were longer when patients underwent microsurgical biopsies as opposed to frameless robot-assisted stereotactic biopsies. More often than stereotactic biopsy patients, microsurgical patients needed more perioperative blood transfusions and neurological impairments [26]. A recent metanalysis found that when 99 pediatric patients with brainstem lesions underwent frameless, robot-assisted biopsies there was not a single case of procedure-related mortality and 100% of the biopsies resulted in successful diagnosis [28].

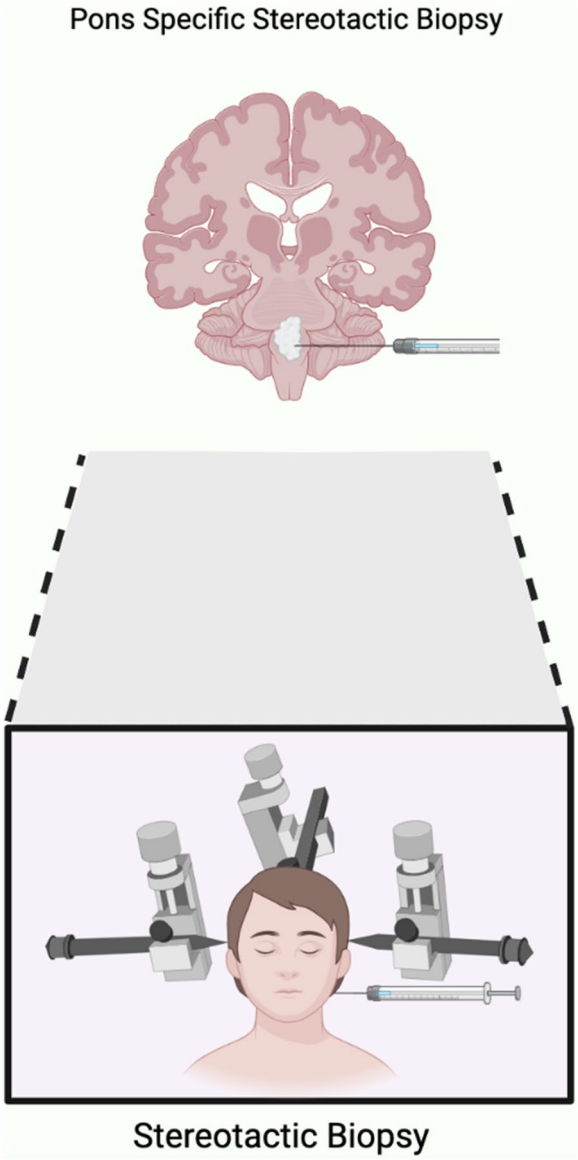

Fig. 3 Stereotactic biopsy offers a feasible technique for collecting tumor tissue in a location historically deemed too dangerous to operate on [5, 25, 26]. Again, while this figure shows a pontine tumor with well-defined borders in, this is hardly the case in DIPG

Although, it's still important to note that approximately 10% of patients experienced temporary complications following the biopsy procedure [28]. Most of these complications were radiologic hemorrhages [26, 29]. However, radiologic hemorrhages are reported in 6–15% of all robot-assisted brain biopsies in adults and children [30]. Therefore, the proximity of DIPG to the brainstem does not seem to dramatically increase the risk of hemorrhage. There were also some cases of cranial nerve palsy [31] involving the hypoglossal, facial, and abducens nerves

[30]. These cases suggest that despite the programmable nature of the frameless robot-assisted biopsy, the cranial nerves are still vulnerable to injury [30]. Though once reserved for cases with questionable diagnosis, biopsy has now emerged a relatively safe part of DIPG diagnosis [25], with frameless robot-assisted stereotactic biopsy serving as a minimally invasive and effective diagnostic and research technique [26].

Radiation therapy

For patients with DIPGs, surgical resection is not an option. Because of this, radiation therapy is the primary form of treatment. Steroids, specifically dexamethasone, are administered to help stabilize the blood–brain barrier before radiation therapy [16]. Conventionally fractionated radiation therapy is typically administered to the tumor for a total amount of 54 Gy across six weeks, whereas hypo-fractionated radiation therapy uses 39 Gy with fewer fractions. Both treatments have similar outcomes [16]. Thorough training is necessary for families to be able to manage the physical side effects of the treatments for the patients. Despite the advancements in radiation therapy (RT) research over the past 20 years, overall outcomes for survival have not significantly changed. A large systematic review examining radiation therapies found that the mean median overall survival was a year for conventional RT regimens, almost 8 months for hypo-fractionated RT regimens, and 10 months for RT hyper-fractionated regimens [32]. Professionals recommend that patients and families combine neuro-oncology and palliative care to maximize performance during treatment [16]. While radiation therapy remains the mainstay of treatment as it temporarily improves neurological symptoms, it lacks targeted control [33]. It has been reported that radiation therapy can increase the permeability of tumor blood vessels which increases tumor cell death. It has been argued that future radiation technologies must target tumor cells, rather than endothelial cells, which is imperative to improving survival rates among patients with DIPGs [33].

Chemotherapy

In addition to radiation therapy, clinical trials are in progress in order to assess the efficacy of chemotherapeutic agents as DIPGs treatment [34]. Different chemotherapeutic strategies have not demonstrated an improvement in survival rates for patients when compared to radiation therapy alone. Administering chemotherapy adjuvant to radiation therapy is not recommended outside clinical trials [11]. It has been hypothesized that a lack of intratumoral penetration prevents systemic chemotherapy from helping DIPG patients; however, other trials investigating intratumoral chemotherapy pharmacokinetics in DIPG that used gemcitabine have provided more positive preliminary evidence [35]. More recent research has reinforced the finding that in DIPGs, the blood–brain-barrier is frequently intact, restricting the delivery of systemically administered therapies and leading to a decreased effective concentration of therapeutic agents in the tumor [11]. The efficacy of chemotherapy could possibly be improved by the simultaneous use of efflux inhibitors and should be considered in future clinical trials [11].

Emerging treatments

Academic research on DIPG in the pediatric population has been hindered due to a shortage in tumor cultures and inadequate experimental models [36]. However, emerging innovations in the fields of microbiology and genetics have illuminated potential effective therapeutic strategies that are steering a new wave of oncological treatment in the clinical setting. Previous investigations have identified a clear link between histone H3 alterations and DIPG: H3F3A, which encodes for histone H3.3, and HIST1H3B, which encodes for histone H3.1, are found to have undergone an Lys27Met amino acid substitution in over 80% of patients analyzed with the malignant tissue [37]. As such, Panobinostat, a multi-histone deacetylase inhibitor, has recently found itself to be a promising pharmaceutical intervention for DIPG. Pre-clinical animal studies have shown a marked effect of Panobinostat, in which the control group has comparatively exhibited a ~6.5-fold greater growth than mice treated with a therapeutic dose [36]. Overall, these results have translated to significant prolonged survival in mice treated with Panobinostat, in comparison with the control cohort. Similarly, the pharmaceutical drug ONC201 is a dopamine receptor D2 antagonist that has recently shown clinical response in patients with DIPG [38]. ONC201, which penetrates the blood–brain barrier, has shown to have an agonist effect on mitochondrial Caseinolytic protease, driving apoptosis through the degradation of mitochondrial respiratory chain enzymes [39]. Since its approval in a pre-clinical context, DIPG patients who have utilized ONC201 as a treatment following radiation have sustained a progression-free state for approximately 53–81 weeks [38]. Complete regression of the tumor has been exhibited in a small percentage of patients as well. Clearly, these outcomes prompt further clinical studies to examine ONC201 in pediatric populations.

Furthermore, the inclusion of viral treatments in the treatment plan of patients with DIPG is rapidly surging as an alternate therapeutic approach. Historically, adult patients with recurrent malignant gliomas have participated in investigations that imposed a dose-escalation strategy to assess DNX-240, an oncolytic adenovirus [40]. The results of the trials have displayed that a single

intertumoral dosage of DNX-2401 promoted immune-cell infiltration in the microenvironment of the tumor cells, generated diverse tumor responses, and potentially extended survival rates in a small percentage of patients [40]. Since then, DNX-240 has been explored in the context of DIPG, which demonstrates a direct oncolytic action against DIPG tumor cells, triggers apoptotic immune responses, and interacts synergistically with radiation therapy [41]. Despite the demand for additional studies to evaluate the effectiveness of DNX-240, the anatomical site of the brain-stem tumor appears to be difficult to access, and there are further concerns regarding procedural complications and inflammation because of virotherapy (Fig. 4).

In addition to histone demethylase inhibitors and immunotherapeutic treatments, other categories of epigenetic modifying treatments may be therapeutically effective for treating DIPG, either alone or in combination once they are approved for use in clinical settings. As more knowledge is acquired pertaining to different CNS malignancies, immunotherapeutic treatments, such as chimeric antigen receptor (CAR) T cells, are giving rise to the approaching wave of DIPG clinical trials. Notably, recent analyses have shown that the DIPG microenvironment is fundamentally distinct from that of adult glioblastomas; in that it is neither immunosuppressive nor immunoinflammatory [42]. Additionally, following its ground-breaking success in treating leukemia, CAR T cells are especially promising in the absence of inherent immunosuppression [43]. Presently, pre-clinical studies utilizing CAR T cells directed against GD2, a disialoganglioside that expressed abundantly in histone H3 alterations, eradicated tumors in mice models [44]. Following a different trajectory, natural agents that potentiate DIPG tumor cell proliferation and cell cycle arrest have been further explored utilizing molecular techniques. The compounds in question were Brefeldin A, an antiviral antibiotic, Chaetocin, an inhibitor of histone methyltransferases, Combretastatin A4, a microtubule polymerization inhibitor, Gracillin, a potential ATP synthesis suppressor, Protodioscin, a promoter of testosterone, and Tubercidin, a polymerase inhibitor [8]. The inhibitory effects of these compounds led to the identification of two novel cellular factors—Eukaryotic Translation Initiation Factor 3 Subunit C-Like (EIF3CL) and Fibronectin 1 (FN1)—both of which are crucial for the survival of DIPG tumor cells and can potentially be utilized as critical therapeutic targets for future clinical trials [8]. Although other eukaryotic translation initiation factors have been thoroughly researched in a variety of malignancies, it is uncertain what function EIF3C serves in cancer cells, aside from aiding in the down regulation of phosphorylation of AMPKα and NF-κB p65 proteins [8]. Ultimately, it is important to take into consideration that only a few commercially patient-derived DIPG cell lines are accessible for future application of all these novel factors that are emerging today.

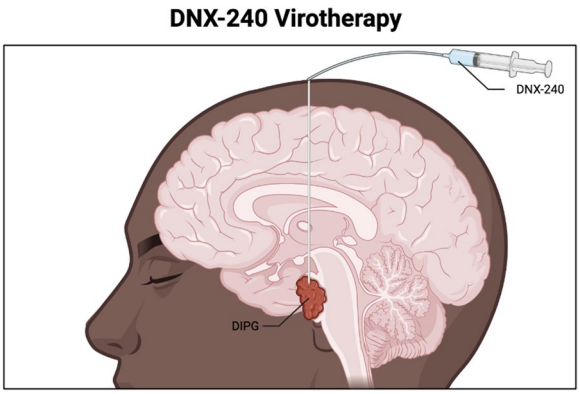

Fig. 4 The use of DNX-2401, an oncolytic adenovirus, promotes immune cell infiltration of the tumor environment, potentially increasing survival rates [40, 41]

Conclusion

Diffuse intrinsic pontine glioma is an aggressive, brain stem astrocytoma usually found in the ventral pons. 80% of DIPG patients show evidence of a detrimental histone mutation known as H3K27M. The delicate location of this tumor previously rendered biopsy impossible. However, in more recent years, the minimally invasive stereotactic biopsy has been implemented as an important diagnostic and research tool in cases of pediatric DIPG. Still though, surgical resection is not possible; therefore, other forms of therapy must be carefully considered. While radiation therapy has been shown to reduce severity of symptoms, it lacks localized control. Few chemotherapy regimens have showed positive outcomes in DIPG patients as these drugs are stopped by a hypothesized lack of intratumoral penetration. The intact blood–brain barrier restricts delivery of chemotherapy agents. However, new pharmaceuticals like Panobinostat and ONC201 show promise. Additionally, viral agents like DNX-240 have been explored to create direct oncolytic action against DIPG tumor cells. Finally, with the well-known histone mutation H3K27M in mind, epigenetic treatments may prove to be the most adequate DIPG therapies. Diffuse intrinsic pontine glioma is a heartbreaking fate for any child to fall victim to. It is essential that scientists continue to explore treatment options to prolong and save the lives of young DIPG patients.

Abbreviations

DIPG	Diffuse intrinsic pontine glioma
HGG	High-grade gliomas
CSF	Cerebrospinal fluid
CNS	Central nervous system
miRNA	MicroRNA
CT	Computed tomography
HGA	High-grade astrocytoma
CAR	Chimeric antigen receptor

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CD completed the introduction and conclusion. CD edited all main text sections, compiled all sources, created bibliography, and completed first-round revisions. SW contributed to writing related to the pathology, prevalence, and risk factors. CC authored and edited the overview information. SW created Figs. 1, 2, and 3. GP wrote the diagnosis and imaging techniques section. AD wrote the stereotactic biopsy, radiation therapy, and chemotherapy portions of the paper. DV authored the section regarding emerging treatments. DV created and edited Fig. 4. All authors read and approved the final manuscript. All authors consented to the publication of the final manuscript.

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Competing interests
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