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Diffuse Intrinsic Pontine Glioma: From Diagnosis to Next-Generation Clinical Trials

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Abstract

Purpose of review This review of diffuse intrinsic pontine glioma (DIPG) provides clinical background, a systematic approach to diagnosis and initial care, and synthesizes historical, modern, and future directions for treatment. We present evidence supporting neurosurgical biopsy, early palliative care involvement, limitation of glucocorticoid use, and the leveraging of preclinical DIPG models as a pipeline to next-generation clinical trials.
Recent findings New molecular understanding of pediatric high-grade gliomas has led to the reclassification of DIPG as one member of a family of diffuse gliomas occurring in the midline of the central nervous system that exhibit pathognomonic mutations in genes encoding histone 3 (H3 K27M). DIPG remains a clinically relevant term, though diagnostically the 80% of DIPG cases that exhibit the H3 K27M mutation have been reclassified as diffuse midline glioma, H3 K27M-mutant. Re-irradiation has been shown to be well-tolerated and of potential benefit. Epigenetic targeting of transcriptional dependencies in preclinical models is fueling molecularly targeted clinical trials. Chimeric antigen receptor T cell immunotherapy has also demonstrated efficacy in preclinical models and provides a promising new clinical strategy.
Summary DIPG is a universally fatal, epigenetically driven tumor of the pons that is considered part of a broader class of diffuse midline gliomas sharing H3 K27M mutations.

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Radiation remains the standard of care, single-agent temozolomide is not recommended, and glucocorticoids should be used only sparingly. A rapid evolution of understanding in the chromatin, signaling, and immunological biology of DIPG may soon result in clinical breakthroughs.

Introduction

While diffuse intrinsic pontine glioma (DIPG) has remained a fatal disease since Wilfred Harris' initial description of a pontine glioma in 1926, we now stand upon the precipice of clinical breakthroughs [1]. Scientific discoveries of the past decade have revolutionized our molecular understanding of DIPG, leading to a new diagnostic classification, "diffuse midline glioma, H3 K27M-mutant," based on pathognomonic histone 3 (H3) K27M mutations present in ~ 80% of DIPG cases [2, 3••, 4••, 5••]. However, as DIPG and other diffusely infiltrating gliomas are not surgically resectable and many children are diagnosed based on the radiographic criteria alone, the molecular characteristics of each tumor are often not evaluated [6–8]. A lack of tissue for diagnosis and research has hampered progress; in comparison, other routinely resected pediatric central nervous system (CNS) tumors have been molecularly subgrouped with next-generation sequencing. Such granular subtype classifications in other pediatric CNS malignancies are beginning to enable tailored therapeutic approaches [9–11]. However, the combined power of new experimental models of DIPG and the demonstrated safety of neurosurgical biopsy has provided an avenue for translating preclinical testing to next-generation molecularly and immunologically targeted therapies that may soon make an impact on the lives of children with DIPG [12, 13•, 14, 15••, 16•, 17–20, 21•, 22–27].

Epidemiology

DIPG accounts for approximately 10% of all CNS tumors and 80% of all brainstem gliomas occurring in children, affecting ~ 300 children per year in the United States (US) [28]. The median age at diagnosis is 6 to 7 years with a relatively equal sex distribution [29•, 30, 31]. With a median overall survival of only 9–11 months, DIPG represents the leading cause of brain tumor–related death in children [29•]. The median progression-free survival is 7 months and survival beyond progression is 2–4 months [29•]. Considering the median-affected age, the incidence, and the fatal prognosis, each year DIPG is responsible for approximately 24,000 years of potential life lost in the US. Rarely, DIPG also occurs in adults.

Diagnostic evaluation

Children affected by DIPG typically present following a median of 1 month of symptoms, although many present with as few as several days of symptoms; and occasionally, prodromes have been reported to be as long as 16 months [30]. Children frequently present with a triad of symptoms including ataxia, pyramidal tract dysfunction, and an abducens nerve (cranial nerve VI) palsy. The abducens palsy is present in the vast majority of children at diagnosis and is usually the first sign of DIPG [32]. In general, any potentially related symptoms

lasting longer than 6 months should prompt a broader differential of possible diagnoses including pilocytic astrocytoma, embryonal tumor, demyelinating disease, or vascular disease. In contrast to DIPG, pilocytic astrocytomas (WHO grade I) are most often exophytic and well-circumscribed, display a cyst/mural nodule formation, and are enhanced with contrast on magnetic resonance imaging (MRI). While DIPG most often originates in the ventral pons and presents acutely, exophytic low-grade gliomas of this region are more commonly tectal, pontomedullary, or cervicomedullary and present with indolent headaches or feeding intolerance [33]. Embryonal tumors commonly have a more heterogenous enhancement pattern on imaging and, at least in other CNS locations, produce extensive peritumoral edema. Large pediatric neuro-oncology practices regularly receive outside referrals for children with DIPG treated as another entity or observed for prolonged periods, as well as cases of suspected DIPG ultimately determined to be another diagnosis. Demyelinating processes are relatively rare in children and can often be distinguished from malignancy with MRI diffuse tensor imaging (DTI) fiber tracking [34].

The best diagnostic study to evaluate a child with suspected DIPG is an MRI of the brain with and without contrast, which will demonstrate an expanded pons and encasement of the basilar artery. The T2 FLAIR MRI sequence typically demonstrates signal in greater than 50% of the ventral pons (basis pontis; Fig. 1). Classically, DIPG does not exhibit contrast enhancement on T1 post-contrast images, though not infrequently there will be some areas of enhancement especially around foci of necrosis. Advanced MRI sequences may play a role in managing DIPG; one report indicates that apparent diffuse coefficient (ADC) images may distinguish distinct prognostic groups, and patients with high ADC values (> 1300) exhibited improved survival [35]. While the epicenter and origin of DIPG is within the pons, regional dissemination into the cerebellum, and even distant spread within the central nervous system, can be present at diagnosis. Dissemination throughout the central nervous system is common over the disease course; in a post-mortem review, disease was identified in the medulla (63%), midbrain (63%), lateral ventricles (63%), cerebellum (56%), thalamus (56%), frontal lobe (25%), and hippocampus (25%), as well as infratentorial leptomeningeal disease in 31% and supratentorial

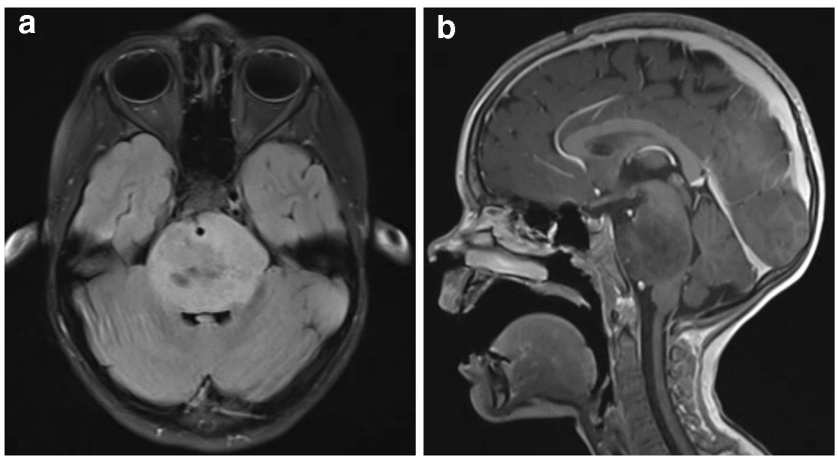

Fig. 1. MRI images of a radiographically classic DIPG, including **a** axial T2 FLAIR and **b** sagittal T1 post-contrast images. Diffuse enlargement of the ventral pons and encasement of the basilar artery are classic signs.

leptomeningeal disease in 25% of patients [36]. Spinal cord disease at diagnosis is also possible, so we recommend MRI of the total spinal cord with and without contrast be performed in the event of any potentially related symptoms. Ongoing consideration of spinal imaging is warranted as DIPG can spread aggressively, even early in its clinical course. Historically, lumbar puncture has not been performed routinely in children with DIPG but considering the incidence of metastatic disease, it may be reasonable and is likely clinically safe to perform in children without evidence of hydrocephalus. Furthermore, while DIPG is not currently diagnosed via lumbar puncture, the advent of testing for circulating tumor DNA (ctDNA, detecting the H3 K27M mutation) soon may allow institutions without neurosurgical expertise in DIPG biopsy to evaluate molecular characteristics of this disease via CSF [37•, 38, 39]. Finding the H3 K27M mutation enables better prognostication for families and allows for consideration of early phase trials that may only be available for particular molecular subgroups.

Prior to the 2016 change in WHO nomenclature, DIPG histological grading ranged from WHO grades II to IV, although histological grade did not correlate with prognosis [2, 40]. However, the 2016 WHO CNS tumor reclassification defined a new entity that encompasses 80% of DIPG tumors: diffuse midline glioma, H3 K27M-mutant (DMG), which is by definition grade IV [2]. Many institutional and commercial sequencing platforms are able to identify the pathognomonic K27M mutations in the histone 3.3 (H3.3) gene *H3F3A*, histone 3.2 (H3.2) gene *HIST2H3C*, and histone 3.1 (H3.1) genes *HIST1H3B/C*, though the most cost-effective test is immunohistochemistry for the H3 K27M mutation (which does not distinguish between H3.3, H3.2, or H3.1 mutant variants) [41, 42]. Because the H3 K27M mutation results in dysfunction of the polycomb repressive complex II (PRC2) and subsequently in H3 K27 hypomethylation, immunostaining for H3 K27-me3 is complementary for H3 K27M-mutant gliomas of the pons and diffuse gliomas found in other midline structures such as the thalamus and spinal cord [43, 44]. The H3.1 variant occurs at a younger median age compared to the H3.3 variant, is more prevalent in females, and is only found in pontine DMG [45••]. The ~ 20% of DIPG tumors that do not express an H3 K27M mutation are not encompassed by the H3 K27M-mutant DMG definition and should not be overlooked as an important subgroup of DIPG tumors whose biology requires dedicated study.

Current treatments

In order to stabilize neurologic symptoms, dexamethasone is the most common initially prescribed treatment for children with newly diagnosed (or suspected) DIPG. A majority of children do not have hydrocephalus or require emergent neurosurgical intervention. A minority of children, either due to prolonged periods of symptom observation, large evolving necrotic centers, or biologically rapid disease, require emergent radiation and/or treatment of hydrocephalus (e.g., with a third ventriculostomy) [46]. Radiation oncologists should be consulted immediately even if a period of diagnostic evaluation and emotional preparation for families is planned prior to the initiation of radiotherapy. Stereotactic needle biopsy should be considered if the imaging appearance is not classical or if a tissue diagnosis will enable possible enrollment on a

molecularly stratified clinical trial. Molecular findings are required for some current clinical trials, and a minority of children may be found to have clinically actionable mutations even outside of clinical trials. The safety of pontine biopsy at experienced centers is highlighted in several reports, including a prospective evaluation of 50 children biopsied at 23 institutions that reported no procedure-related deaths and infrequent toxicity, with two grade 3 adverse events (apnea, hypertension) during the procedure and one subject with a neurological toxicity from which they did not recover (hemiparesis) [21•]. Experienced neurosurgeons can provide the most appropriate counseling, but, in brief, while neurological adverse events are rare, they can be severe [19, 21•, 24, 25, 27]. Biopsy should not inherently delay radiation as radiation planning can be done while neurosurgical biopsy is being considered.

Dexamethasone best serves as a bridge through possible neurosurgical biopsy and the initiation of radiation, but should be weaned off completely as quickly as tolerated due to adverse effects of corticosteroids including impaired sleep, impaired wound healing, increased appetite/weight gain, psychological and behavioral disturbances, diabetes mellitus, immunosuppression, and Cushing syndrome [47–50]. Dexamethasone may have an even more detrimental effect relating to the treatment of DIPG, as corticosteroids close the blood–brain barrier and thereby potentially limit tumor tissue penetration of potential systemic therapies [51, 52]. Furthermore, dexamethasone causes a specific gene-expression pattern in high-grade gliomas that portends a worse overall survival [53•, 54]. Ultimately, while dexamethasone may have a role in short bursts, children on prolonged steroids are at high risk for decreased quality of life. Tachyphylaxis to corticosteroids represents another reason to minimize corticosteroid use. The planned strategy for corticosteroid use and the expected side effects represents a conversation best initiated early with families and patients.

A critical early consideration should be the consultation of pediatric advanced care or pediatric palliative care specialists. Offering palliative care services to all patients with DIPG or DMG early in the course provides personalized support for the immediate and ongoing physical, psychological, social, and other effects this presently lethal prognosis will have on a family. Combined neuro-oncologic and palliative care support maximizes how patients and families function during their treatment and even can help to identify disease-related changes before otherwise clinically or radiographically suspected progression [55].

Focal radiotherapy remains the standard of care for children with DIPG and increases overall survival by ~ 3 months; without radiotherapy, overall survival is only ~ 5 months [56]. Radiation is most commonly delivered using photon radiotherapy conformally delivered to the tumor at 54 Gy in 1.8-Gy daily fractions over 6 weeks. A hypo-fractionated approach using 39 Gy in 13–16 fractions appears to have similar outcomes and results in less medical burden, especially for young children requiring sedation [57, 58]. A hyperfractionated approach to 78 Gy did not provide a survival benefit and potentially increased steroid dependence and a severely hypo-fractionated approach of 25 Gy in only 5 fractions may have shortened survival and increased radiation necrosis [59, 60]. After disease progression, re-irradiation may also be considered. Re-irradiation regimens of approximately 25 Gy over 10 fractions

repeatedly have been demonstrated to be safe and suggest a modest survival benefit, as well as a stabilization or improvement in symptoms [61–64].

More than 200 clinical trials of conventional cytotoxic and myeloablative chemotherapy have failed to improve survival in children with DIPG [65]. Radiosensitizing agents during radiotherapy have thus far failed to improve survival [66–68]. Likewise, intensive chemotherapeutic treatment regimens, including myeloablative dosing requiring stem cell transplantation, have not shown promise [69, 70]. Despite modest efficacy in adult high-grade gliomas, single-agent temozolomide does not improve DIPG outcomes in either conventional or metronomic dosing [71–74]. Most recently, gemcitabine, capecitabine, several tyrosine kinase inhibitors most often targeting VEGF or EGFR, and an EGFR monoclonal antibody have been evaluated in DIPG without major improvements in survival, although the EGFR inhibitor gefitinib's 1-year median OS of 56% is higher than many historical reports [75–83]. This overall lack of response to traditional chemotherapeutic agents is concordant with a broad lack of response to most cytotoxic chemotherapeutics of DIPG cell cultures in drug screens, and underscores the need for therapies targeting the unique biology of DIPG and an effective means by which to deliver those putative therapies to this cancer with a relatively intact blood–brain barrier [20].

Future treatments

The advent of genetically engineered and patient-derived experimental models now provides a critical avenue for deepening our biological understanding of DIPG and preclinical therapeutic testing [17, 18, 22, 23, 26]. Epigenetically targeted agents are of particular interest, both conceptually and empirically from preclinical drug screens [20]. Supported by preclinical studies, the clinical efficacy of the HDAC inhibitor panobinostat is now being evaluated in several clinical trials (e.g., NCT02717455) [20]. A subsequent preclinical study of epigenetic strategies identified several other agents that target oncogenic transcription, such as through CDK7 blockade or bromodomain inhibition [15••]. While not ready for clinical translation, jumonji demethylase inhibitors also appear to exhibit modest preclinical benefit, enforcing the concept of targeting aberrant transcription in DIPG [84].

Immunotherapeutic agents including vaccine therapies, oncolytic viruses, checkpoint blockade, and chimeric antigen receptor (CAR) T cells account for the upcoming next wave of DIPG clinical trials as more experience is garnered in other CNS tumors [13•, 85•, 86]. Critically, recent independent evaluations revealed the DIPG microenvironment to be neither highly immunosuppressive nor inflammatory, making it fundamentally different from adult glioblastoma [14, 16•]. In the absence of innate immunosuppression, CAR T cells are particularly promising on the heels of their revolutionary benefit in leukemia [87]. In preclinical in vivo studies, CAR T cells targeting GD2, a disialoganglioside highly expressed in H3 K27M-mutant DMG, eradicated H3 K27M-mutant DMG tumors in xenograft models; additional targets for CAR T cell therapy such as B7H3

have also recently come to light [88•, 89•]. A clinical trial of GD2-specific CAR T cell therapy for DIPG is presently in preparation. Currently, clinical trials of HER2-specific CAR T cells (BrainChild-01, NCT03500991) and EGFR806-specific CAR T cells (BrainChild-02, NCT03638167) are evaluating locoregional delivery of CAR T cells in children with refractory or recurrent CNS tumors. While these have excluded DIPG, their insight into CNS inflammatory responses will inform BrainChild-03, a clinical trial of B7-H3-specific CAR T cells presently in preparation for children with DIPG.

Finally, novel therapy delivery strategies are emerging including convection-enhanced delivery (CED), in which catheter tips are neurosurgically inserted into the pons and a pressure gradient is used to deliver regional therapy [90]. While DIPG is often a metastatic disease, the most critical pontine disease does likely have innate protection from systemic chemotherapy, such as through the blood–brain barrier or intrinsic high pressure, so CED is currently being evaluated in early phase clinical trials [91].

Conclusion

DIPG remains a universally fatal disease with a median survival of under 1 year. While the diagnosis is often made by MRI, neurosurgical biopsy is safe and is becoming more common in an effort for improved diagnosis, prognostication, and therapeutic targeting. The discovery of H3 K27M mutations has revolutionized our understanding of DIPG biology, creating the new diagnostic class H3 K27M-mutant diffuse midline gliomas, which includes thalamic and spinal tumors with similarly dismal prognoses. Radiation remains the mainstay of therapy, and re-irradiation at the time of tumor progression appears safe and can confer modest improvements in symptoms and in survival. Glucocorticoid use should be carefully minimized, and single-agent temozolomide has no role in DIPG therapy. The H3 K27M mutation results in transcriptional dependencies that may be leveraged with epigenetically targeted agents, some of which are currently being evaluated in clinical trials. Complimentary preclinical models of DIPG form the foundation of a preclinical to clinical pipeline as we further investigate the role of immunotherapies and, ultimately, combinatorial approaches targeting both cell-intrinsic vulnerabilities and microenvironmental dependencies in the search for a cure of this seemingly intractable childhood brain cancer.

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Compliance with Ethical Standards

Conflict of Interest

Nicholas A. Vitanza declares no potential conflicts of interest. Michelle Monje has a pending patent entitled "CAR T cell therapy to treat H3K27M midline gliomas."

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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