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Diffuse intrinsic pontine glioma (DIPG): A review of current and emerging treatment strategies

Luke J. Weisbrod [a], Anand Thiraviyam [b], Raghupathy Vengoji [b], Nicole Shonka [c d], Maneesh Jain [b c e], Winson Ho [f], Surinder K. Batra [b c e], Afshin Salehi [a g]

[a] Department of Neurosurgery, University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA
[b] Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA
[c] Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA
[d] Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA
[e] Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA
[f] Department of Neurosurgery, University of California San Francisco, San Francisco, CA, 94143, USA
[g] Division of Pediatric Neurosurgery, Children's Nebraska, Omaha, NE, 68114, USA

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Highlights

- DIPG poses a lethal prognosis due to a lack of safe surgical resection and the ineffectiveness of current therapies.
- The H3 K27 substitution of lysine to methionin leads to significant dysfunction of epigenetic programming and signaling.
- An increased understanding of DIPG at the molecular level will help provide fruitful targets for novel therapies.

Abstract

Diffuse intrinsic pontine glioma (DIPG) is a childhood malignancy of the brainstem with a dismal prognosis. Despite recent advances in its understanding at the molecular level, the prognosis of DIPG has remained unchanged. This article aims to review the current understanding of the genetic pathophysiology of DIPG and to highlight promising therapeutic targets. Various DIPG treatment strategies have been investigated in pre-clinical studies, several of which have shown promise and have been subsequently translated into ongoing clinical trials. Ultimately, a multifaceted therapeutic approach that targets cell-intrinsic alterations, the micro-environment, and augments the immune system will likely be necessary to eradicate DIPG.

Introduction

Diffuse intrinsic pontine glioma (DIPG), a subset of diffuse midline glioma (DMG), are high-grade glial tumors comprising at least 50% of the pons often presenting with a clinical triad of long-tract signs, ataxia, and isolated or multiple cranial neuropathies [1]. DIPGs have an incidence of 1.78 per 100,000 population, with approximately 300 children diagnosed with DIPG in the United States (U.S.) each year [2,3]. Although rare, gliomas collectively represent the highest cause of cancer-related deaths in patients under 19 years of age [2]. DIPGs comprise approximately half of all pediatric high-grade gliomas (HGG) [4]. These tumors occur almost exclusively in children, with a peak incidence between the ages of 6–8 years [5]. The median survival of DIPG is less than 1 year, and the overall survival is less than 1% at 5 years [6].

Genetically, the histone 3 (H3) tail lysine 27 (K27) post-translational modifications play a significant role in the overall functional properties of deoxyribonucleic acid (DNA), with acetylation and methylation resulting in significant downstream effects [7]. The H3 K27 alteration, as the result of lysine-to-methionine substitution at the amino acid 27 position, leads to significant dysfunction of epigenetic programming and signaling [8,9]. Key epigenetic alterations involved include polycomb repressor complex 2 (PRC2) and its catalytic subunit, enhancer of zeste homolog 2 (EZH2) [10]. EZH2 functions to methylate the histone H3 at the lysine 27 position, resulting in transcriptional silencing [11]. The inhibition of PRC2 results in a reduction in the total H3 methylation [9,12]. The collective H3 K27M hypomethylation has been suggested to decrease differentiation ability and increase cell proliferation potential, inducing the formation of a high-grade tumor [7]. The genetic drivers contributing to the temporal and spatial presentation of DIPG and H3 K27M alteration are felt to be relatively homogenous [13]. A recent study employing single-cell ribonucleic acid (RNA) sequencing of DIPG, however, has given new insight into the cellular and transcriptional architecture of H3 K27M tumors and demonstrated that while most differentially expressed genes were upregulated in H3 K27M DIPG, some were also down-regulated, adding further complexity to its underlying pathophysiology [14].

In 2021, the World Health Organization (WHO) updated the nomenclature for some central nervous system (CNS) malignancies: DMG is now designated “H3 K27M-altered” rather than “H3 K27M-mutant”, to recognize alternative pathophysiologic mechanisms in these tumors [15,16]. Additionally, the term “glioblastoma was retired from the setting of pediatric tumors, as its biology differs from its pediatric counterparts [15]. In contrast to histologically similar lesions in adults, which tend to be restricted to the cerebral hemispheres, the midline anatomic location of DMGs, particularly the brainstem in DIPGs, restricts maximal safe surgical resection, contributing to its poor prognosis. Historically, there were beliefs that stereotactic biopsy of presumed DIPGs was also not a safe surgical option. Recently, stereotactic biopsy has been shown to have minimal effect on mortality within the past couple of decades, reported at 0.6% with a high diagnostic yield of 96.1% [17,18]. Overall morbidity, including transient neurologic deficits, occurred in 6.7–8% of cases and remained permanent in 0.6–3.1% of cases [17,19]. In children older than 3 years of age, radiotherapy can be administered [1]. While radiotherapy may improve outcomes, it often comes at the cost of long-term, late effects in survivors, including endocrine dysfunction [20], radiation necrosis [21], secondary malignancy [21],

hearing loss [22] and neurocognitive dysfunction [23]. In long-term survivors of pediatric brain tumors, neurocognitive dysfunction has been identified as the leading cause of reduced quality of life with a high rate of dementia, especially in those receiving radiation under the age of 2–3 years, which is why radiotherapy is now avoided in this age group [24,25].

Temozolomide is often used concurrently with radiation therapy. Despite its use, no studies have demonstrated a clear role of temozolomide in the setting of DIPG, and it is largely an extrapolation of glioblastoma (GBM) therapy. Studies support a high expression of O6-methylguanine DNA methyltransferase (MGMT) in H3 K27-altered DMGs, contributing to temozolomide resistance in DIPG [26,27]. Despite advances in medical care and pre-clinical and clinical studies, the median overall survival of DIPGs is 9–15 months, a figure that has remained unchanged for decades [28]. In this article, we will outline the genetic pathophysiologic mechanisms that lead to the development of DIPG. We will next review the ongoing clinical trials, pre-clinical studies, and emerging targets in the treatment of DIPG.

Section snippets

Genetics

Diffuse midline gliomas most commonly occur in the pons, but can also occur in the thalamus, other regions of the brainstem, spinal cord parenchyma, or other midline locations within the CNS. In a series of 50H3–K27M mutant patient tumors, 27 DMG's were located within the pons, 20 within the thalamus, 1 in the lower brainstem, and 2 in the spinal cord parenchyma [29]. In a larger series of 547 DMGs, 323 were located within the pons, 3 in the midbrain, 1 in the medulla, and 224 in non-brainstem …

Clinical trials

As previously mentioned, the pontine location of DIPGs within the brainstem restricts maximal safe resection and is not a feasible treatment option. Therefore, the current standard treatment regimen is temozolomide with concurrent external beam radiotherapy at a dose of 54–60 Gy (Gy) with conventional fractionation (1.8–2.0Gy daily, 5 days/week) for 6 weeks if the patient is older than 3 years of age [53]. There are currently 21 actively recruiting clinical trials listed on the clinical trials …

Animal models

Animal models constitute a valuable tool in studying DIPG and are the key to uncovering novel therapeutic vulnerabilities. Historically, given DIPG's rare occurrence and its eloquent location within the brainstem, obtaining DIPG tissue has been difficult and ultimately restricted prior research efforts. The combination of improved mortality/morbidity with biopsy and the aforementioned genetic and epigenetic pathophysiologic discoveries have made it more feasible to develop animal models that…

Pre-clinical studies

Panobinostat is a histone deacetylase (HDAC) inhibitor that has shown promise in multiple myeloma. HDAC inhibitors, such as Panobinostat, have been shown to exert a broad spectrum of anti-tumorigenic effects, including induction of cell cycle arrest, inhibition of angiogenesis, and apoptosis, among others [[143], [144], [145]]. Given its pre-clinical promise, Panobinostat has undergone rapid clinical development and has been approved by the European Medicines Agency (EMA) and FDA for the…

Emerging new targets

A potential future therapeutic option that is currently under development for DIPG and gaining momentum is nanotechnology. Cancers such as lung and liver cancer, more common and accessible types of cancer, initially led the field as recipients of nano-derived therapeutic particles [[178], [179], [180], [181]]. A specific advantage of nanoparticle treatment is that the nanoparticles do not diffuse freely like small molecules and have increased permeability and retention in tumor tissue [182]....

Conclusions and perspectives

DIPGs pose a lethal prognosis due to a lack of safe surgical resection and the ineffectiveness of current drug and radiation therapies. While its prognosis has remained stable for decades, there is reason for optimism with the advent of further understanding of H3 K27M-altered DIPG biology and numerous clinical trials investigating recently translated concepts. Expanding on recent advances in our understanding of DIPG at the molecular level and an increased understanding of the immune...

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Declaration of competing interest

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