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Local delivery methods of therapeutic agents in the treatment of diffuse intrinsic brainstem gliomas

C. Rory Goodwin, Risheng Xu, Rajiv Iyer, Eric W. Sankey, Ann Liu, Nancy Abu-Bonsrah, Rachel Sarabia-Estrada, James L. Frazier, Daniel M. Sciubba, George I. Jallo *

The Johns Hopkins University School of Medicine, Department of Neurosurgery, Baltimore, MD, USA

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ABSTRACT

Brainstem gliomas comprise 10–20% of all pediatric central nervous system (CNS) tumors and diffuse intrinsic pontine gliomas (DIPGs) account for the majority of these lesions. DIPG is a rapidly progressive disease with almost universally fatal outcomes and a median survival less than 12 months. Current standard-of-care treatment for DIPG includes radiation therapy, but its long-term survival effects are still under debate. Clinical trials investigating the efficacy of systemic administration of various therapeutic agents have been associated with disappointing outcomes. Recent efforts have focused on improvements in chemotherapeutic agents employed and in methods of localized and targeted drug delivery. This review provides an update on current preclinical and clinical studies investigating treatment options for brainstem gliomas.

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1. Introduction

Brainstem tumors are heterogeneous and arise from the midbrain, pons, medulla, and upper cervical spine. Comprising 10–20% of all pediatric central nervous system (CNS) tumors with an annual incidence of 200–300 cases in the United States, brainstem tumors have a mean age of diagnosis of 7–9 years with no gender predilection [1,2]. Earlier classification schemes for pediatric brainstem

Abbreviations: CNS, central nervous system; DIPG, diffuse intrinsic pontine gliomas; BBB, blood–brain barrier; CED, convection-enhanced delivery; HESC, human embryonic stem cells; NPC, neural progenitor cells; PDGFR, platelet-derived growth factor receptor; Gd, Gadolinium.

* Corresponding author at: Johns Hopkins Hospital, Division of Pediatric Neurosurgery, Phipps 556, 600 N. Wolfe Street, Baltimore, MD 21287, USA. Fax: +1 410 955 7862.
E-mail address: gjallo1@jhmi.edu (G.I. Jallo).

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Table 1
Classification schemes for pediatric brainstem tumors.

Author	Method utilized to create system	Classification system
Epstein [3]	CT	Intrinsic Diffuse Focal Cervicomedullary Exophytic Anterolateral into cerebellopontine angle Posterolateral and into brachium pontis Disseminated Positive cytology Positive myelography
Epstein and McCleary [4]	CT, MRI, and surgical observation	Diffuse Focal Cervicomedullary
Stroink et al. [5]	CT	Group I—dorsal exophytic glioma Group IIa—intrinsic brainstem tumors, hypodense, no enhancement Group IIb—intrinsic brainstem tumors, hyperdense, contrast enhancing exophytic Group III—focal cystic tumor with contrast enhancement Group IV—focal intrinsic isodense contrast enhancement
Barkovich et al. [6]	MRI	Location (midbrain, pons, medulla) Focality (diffuse or focal) Direction and extent of tumor growth Degree of brainstem enlargement Exophytic growth Hemorrhage or necrosis Evidence of hydrocephalus
Albright [7]	MRI	Focal (midbrain, pons, medulla) Diffuse
Fischbein et al. [8]	MRI	Midbrain Diffuse Focal Tectal Pons Diffuse Focal Medulla Diffuse Focal Dorsal Exophytic
Choux et al. [9]	CT and MRI	Type I—diffuse Type II—intrinsic, focal Type III—exophytic, focal Type IV—cervicomedullary
Rubin et al. [89]	Clinical features and MRI	Cervicomedullary Exophytic Cystic Focal Diffuse

tumors are based on CT imaging and observation, while more recent ones rely on a combination of both CT and MR imaging. All schema differentiate tumors into focal or diffuse growth patterns, with further subdivisions based on their origin within the brainstem, the presence or absence of an exophytic component, and the presence of hydrocephalic or hemorrhagic features. The basis for these classification schemes is to help guide operative vs. non-operative management of these lesions. In general, tumors with well-defined borders and focality are considered more surgically amenable, while those with diffuse, infiltrating patterns are less likely to benefit from surgery (Table 1) [3–9].

Of all pediatric brainstem tumors, diffuse intrinsic pontine gliomas (DIPGs) comprise the vast majority of cases (60–75%). Children with these infiltrating tumors often present with progressive symptoms such as weakness, ataxia and multiple cranial nerves deficits [10,11]. Prognosis is dismal with a median survival less than 12 months, and the surgical role is limited to diagnostic biopsy in some cases. Even the role for stereotactic or open biopsy in these patients has been controversial. In patients with classic DIPG diagnosed through radiographic and clinical criteria, decreased morbidity without biopsy has been shown [12]. In recent years, however, reconsideration of surgical biopsy has been advocated by some to rule out masquerading diagnoses, obtain definitive histopathological diagnosis for clinical trial entry and/or to obtain tissue for molecular genotyping [13,14].

The mainstay of treatment of DIPG has been radiation therapy (54 Gy in daily fractions of 1.8 Gy) [15–17]. Outcomes have not shown a clear survival benefit, but improved progression-free survival and transient improvements in neurological function with radiotherapy, as well a relative lack of other therapeutic options have led to its widespread use in the treatment of DIPG. Varied radiation treatment doses have also been attempted with both hypo- and hyper-fractionated regimens demonstrating disappointing clinical responses similar to conventional strategies [18–21].

Treatment of childhood brainstem gliomas with chemotherapeutic agents has been particularly challenging given the lack of tumor-specific targets and the difficulty in delivering systemic, clinically relevant drug volumes due to limitation by the blood–brain barrier (BBB). To date, systemic administration of chemotherapeutic regimens in a variety of temporal combinations with radiotherapy have been assessed in clinical trials for patients diagnosed with brainstem gliomas [22–31]. Unfortunately, these multimodal therapeutic studies have not demonstrated a significant prolongation in survival. Therefore, treatment modalities such