Chapter 14
Radiation and Chemotherapy for Brainstem Tumors

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Abbreviations

[^{124}I]-8H9	Radioisotope iodine 124 conjugated to antiglioma monoclonal antibody 8H9
BBB	Blood-brain barrier
BMP	Bone morphogenetic protein
BRD4	Bromodomain containing protein 4
CDK7	Cyclin dependent kinase 7
CED	Convection enhanced delivery
CNS	Central nervous system
CSF	Cerebrospinal fluid
DIPG	Diffuse intrinsic pontine glioma
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
FLAIR	Fluid attenuated inversion recovery
HDAC	Histone deacetylase
HR	Hazard ratio
IgG1	Immunoglobulin G-1
IL13-PE	Interleukin-13-pseudomonas exotoxin
MRI	Magnetic resonance imaging
N	Number
NF-I	Neurofibromatosis type I
OS	Overall survival
PCV	Procarbazine, lomustine and vincristine
PEG-Intron	Pegylated interferon alpha-2b
PFS	Progression-free survival
TPCV	6-thioguanine, procarbazine, lomustine and vincristine

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TTP	Time to progression
WHO	World Health Organization
WT	Wild type

14.1 Introduction

Brainstem gliomas are a heterogeneous group of tumors. Because clinical presentation and prognosis can differ significantly, treatment options vary, and a risk-to-benefit analysis is employed [1, 2]. In children, brainstem gliomas are often distinguished as diffuse intrinsic pontine glioma (DIPG) or non-DIPG. The biology and prognosis of adult "DIPG" differ from pediatric DIPG; unlike non-DIPG brainstem gliomas in children that are frequently low-grade, adult non-DIPG brainstem gliomas are frequently malignant and portend a poor prognosis. Therefore, differences in prognosis between adult DIPG and non-DIPG are not as evident as in the pediatric population. Treatment recommendations consider surgical resectability, clinical presentation, radiographic appearance, and tumor grade. Other factors such as length of time of symptoms, rapidity of symptom progression, present or impending cerebrospinal fluid (CSF) obstruction, patient age, and other prognostic factors may play a role in treatment decisions.

DIPG are diffuse, infiltrative lesions with tumor cells intertwined amongst critical neural structures in the brainstem and, therefore, lack a realistic surgical option. Histologically, these lesions are World Health Organization (WHO) Grades II-IV gliomas. Pediatric patients with typical DIPG tend to have similar outcomes regardless of tumor grade [3], while glioma grading in adults does appear to impact outcome [4]. Additionally, H3K27M mutations are found in up to 80% of children with DIPG [5], yet this mutation does not appear to be as common in the adult disease. The presence of this mutation is *prognostic*, with patients having lower overall survival (OS) compared to those children with wild type (WT) H3 [6, 7]. Despite this, standard treatment regimens remain the same for children with and without these mutations, as no clinically effective therapy has yet been identified; i.e., H3K27M mutations are not yet *predictive* of response. As will be discussed in the chemotherapy section, biopsy with identification of specific mutations, including H3K27M, has led to clinical trials involving molecularly targeted agents with the hope that therapy aimed at specific mutations will be more effective than empiric therapies.

In contrast to the malignant biology observed in DIPG, pediatric non-DIPG brainstem gliomas frequently display a more benign nature and clinical course. Non-DIPG brainstem gliomas are further categorized as focal, dorsal exophytic, or cervicomedullary gliomas [8]. Whereas diffuse brainstem gliomas most frequently occur in the pons, low-grade, well-circumscribed gliomas typically involve midbrain and medulla locations [9], suggesting oncogenic contributions from the microenvironment and different cells of origin. Notably, the survival rates of patients with focal and exophytic brainstem gliomas, which are typically discrete masses, and even cervicomedullary gliomas, which are frequently pilocytic astrocytomas,

are significantly higher than those with diffuse lesions involving the pons, as these tend to be amenable to surgical resection (complete or partial resection or debulking) [1, 10–12].

Adult brainstem gliomas account for <2% of all adult gliomas [4, 13, 14], and approximately 60% have their epicenter in the pons [15]. Although the data is limited, adults with diffuse pontine gliomas tend to have modestly better outcomes than children with DIPG [13]. In contrast to typical pediatric DIPG in which median survival is less than 1 year from diagnosis, median survival for adults with brainstem glioma is 30–49 months [4, 16], although the number of patients included in adult studies are small, and it is unclear how many patients display the characteristic clinical and radiographic findings of typical pediatric DIPG. In adult brainstem glioma, there is an association between the presence of contrast enhancement with survival (worse outcomes with increasing grade and contrast-enhancement) [4, 16], although this correlation is not clear in pediatric DIPG [17]. However, differences in outcome between adult and pediatric DIPG do not appear solely related to differences in histologic grade [18].

For clarity, this chapter will be organized to discuss the treatment of (a) pediatric DIPG, (b) pediatric non-DIPG brainstem gliomas, and (c) adult brainstem gliomas.

14.2 Treatment of Pediatric Diffuse Intrinsic Pontine Glioma (DIPG)

There are limited therapeutic options for patients with DIPG. The *only* therapy that has demonstrated significant, albeit temporary, clinical benefit to children with DIPG is radiation therapy, which remains the standard of care [17, 19]. Patients often present with rapid onset (days-to-weeks) and progressively worsening symptoms. Glucocorticoids are typically initiated at diagnosis or early in the radiation course to alleviate symptoms attributed to peritumoral edema. While radiation therapy is frequently instituted as soon as possible in efforts to relieve or reduce symptoms, a retrospective study demonstrated that the time from diagnosis to the start of radiation therapy did not affect event-free survival (EFS) or OS [20].

14.2.1 Radiation Therapy

The standard therapeutic approach for patients diagnosed with DIPG is external beam radiation therapy, administering 54–60 Gy via focal photon radiation therapy in 180–200 cGy fractions, 5 days per week, over approximately 6 weeks [17, 21–25]. This schedule, applicable to patients with any malignant glioma, has not changed over the past 5 decades and was originally established based upon the convenience of the 5-day schedule and experience of radiotherapists regarding acute tolerability of patients [26]. The total dose of radiation administered is critical for

malignant glioma. In a retrospective study evaluating a dose-effect of 50, 55 or 60 Gy for malignant glioma, there was a direct relationship between increasing dose and increased survival [26]. For children with DIPG, it is generally agreed that doses less than 50 Gy are inadequate, and doses higher than 60 Gy may introduce additional toxicities without added benefit [27]. The gross tumor volume is defined based on T2-weighted, fluid attenuated inversion recovery (FLAIR), and T1-weighted post-contrast sequences, with the clinical target volume including the gross tumor volume and a 1–2 cm margin [20]. Conformal radiation therapy approaches may be used to decrease the volume irradiated and protect critical structures. In a study utilizing fractionated stereotactic radiation therapy, 41 patients (n = 26 adults; n = 15 children) with brainstem gliomas, including DIPG, received fractionated, high precision radiation therapy to a total dose of 54 Gy [27]. The pattern of failure was local in the majority of patients. Despite the heterogeneous group of patients, this study demonstrated the feasibility of fractionated stereotactic radiation therapy to improve target point precision and decrease exposure to critical structures. However, DIPG commonly extends beyond the pons, and some authors advocate more extended, rather than more precise, radiation fields [3, 28]. In this same context, most experts agree that there is no role for proton radiation therapy approaches in typical DIPG patients.

Radiation therapy improves neurological symptoms in approximately 75% of patients with DIPG and increases OS from a median of 4.7 months [29] to 8–11 months [17, 21]. Unfortunately, any beneficial anti-tumor effects of radiation therapy are short-lived, with tumor growth or clinical progression generally noted within 3–6 months of completion [17, 19, 30–32]. The pattern of failure is usually local [30], although the tumor is frequently also found outside the radiation field, with leptomeningeal and/or subventricular zone disease detected in most patients at autopsy [28]. Despite these findings at autopsy, craniospinal radiation at diagnosis is not typically performed unless indicated by clinical symptoms.

14.2.1.1 Hyperfractionated Radiotherapy

While there are some variations to the standard dose and schedule for DIPG [33], including higher total doses or alternate schedules, a limited number of studies have been performed to determine the optimal schedule providing the best therapeutic index and clinical benefit [34]. Because there is a known dose-response relationship for radiation in malignant gliomas [26], higher doses have been investigated in children with brainstem tumors. In reviewing the impact of these trials, it is important to note that many initial clinical trials did not distinguish DIPG from other brainstem gliomas. In a study comparing a total dose of 70.2 Gy administered in 117 cGy twice daily fractions over 6 weeks with conventional radiation therapy (total dose was 54 Gy administered in 180 cGy fractions over 6 weeks), OS, EFS and toxicities of the n = 130 patients did not significantly differ (OS 8 months versus 8.5 months,

respectively) [31]. A Phase I/II clinical trial of escalating doses of hyperfractionated radiation therapy initially suggested a trend toward clinical benefit, with increased OS and time to progression (TTP) with increasing total radiation doses of 66–72 Gy; subsequently, the dose was increased to 75.6 Gy [35]. However, while neurological improvement was still noted in about 75% of patients, higher doses of radiation therapy again did not improve the median TTP or OS (7 months versus 10 months, respectively) [35]. The pattern of failure again was local progression, although 6 of 39 patients also had leptomeningeal disease. Notably, more than 60% of patients required steroids for at least 3 months, and 45% had evidence of intratumoral necrosis on imaging. Another study evaluated hyperfractionated radiotherapy doses of 78 Gy in children with brainstem gliomas [36]. Although this dose was relatively well-tolerated, results were similar, with no improvement in patient outcomes, evidence of prolonged steroid-dependency, and apparent radiation necrosis on imaging. In a follow-up study comparing conventional versus hyperfractionated radiation therapy and incorporating cisplatin as a radiation sensitizer in both arms in children with newly diagnosed brainstem gliomas, there was no significant difference in EFS or OS [31]. Thus, given the evidence to date, there is no role for hyperfractionated radiation therapy in this population.

14.2.1.2 Hypofractionated Radiation Therapy

In an effort to shorten the 6-week radiation timeline and reduce the treatment burden, hypofractionated radiotherapy delivered over shorter time periods, usually 3–4 weeks, has been investigated in several studies of children with newly diagnosed DIPG [30, 37]. In a single institution study of 22 children with newly diagnosed DIPG [37], 14 patients received the prescribed dose of 45 Gy in 15 fractions of 3 Gy, while 5 patients required a reduced daily dose due to toxicities, and 1 patient died due to severe intracranial hypertension after two fractions. Median TTP and OS were 5.7 and 7.6 months, respectively. In a second study that was a multicenter retrospective analysis, n = 27 children with newly diagnosed DIPG treated with one of two hypofractionated regimens administered over 3–4 weeks (39 Gy in 3 Gy fractions or 44.8Gy in 2.8 Gy fractions) were compared to a randomly selected matched cohort receiving conventional radiation therapy [30]; TTP and OS were reported as not significantly different between the two groups (TTP 5.0 vs. 7.6 months [p = 0.24], and OS 9 vs. 9.4 months, respectively), although the number of patients was small [30]. In a randomized control study of n = 71 patients comparing hypofractionated therapy (total dose was 39 Gy administered in 3 Gy fractions; 13 fractions over 2.6 weeks) versus conventional radiation therapy (54 Gy in 180 cGy fractions over 6 weeks), median OS for the hypofractionated group was 7.8 months versus 9.5 months in the conventional radiation therapy group [38]. No significant difference in OS (hazard ratio [HR] 1.03) or toxicities were noted between the two groups [34]. Taken together, these studies suggest that shorter radi-

ation treatment periods may be appropriate for some patients, e.g., those needing daily anesthesia; however, although statistically significant differences have not been observed in each study, patient numbers are small, there appears to be a trend toward shorter TTP, and larger, randomized trials are needed.

14.2.1.3 Radiosensitizing Agents

Agents that increase a cancer cell's vulnerability to radiation have been investigated in further attempts to optimize the anti-tumor effects of radiation therapy for DIPG. However, no radiosensitizing agent to date has significantly improved outcomes for this patient population. Cisplatin was one of the earliest agents to be clinically investigated as a radiosensitizer given its ability to potentiate radiation effects preclinically *in vitro* and *in vivo* [39, 40]. In a clinical trial comparing hyperfractionated radiation therapy with and without cisplatin as a radiosensitizer in children with diffuse intrinsic brainstem gliomas, patients receiving cisplatin had a worse outcome compared to those receiving radiation therapy only, suggesting increased toxicity in those receiving combination therapy [41]. Motexafin-gadolinium is another radiosensitizing agent evaluated in children with DIPG [42, 43]. Its metalloporphyrin localizes in tumors and inhibits oxidative stress-related proteins, resulting in a decreased ability to repair radiation-induced damage [44]. Despite its ability to penetrate into the tumor as assessed on magnetic resonance imaging (MRI) scans, addition of Motexafin-gadolinium to conventional radiation therapy did not improve OS in a clinical trial for children with DIPG [43]. Additional chemotherapeutic agents, such as gemcitabine [45] and capecitabine [46] have been evaluated as radiosensitizers and/or given in the adjuvant setting as "chemoradiation" therapy. As with other chemotherapeutic agents, no improvement in outcomes has been demonstrated; furthermore, there is some concern for additional toxicities and potential delays in radiation therapy [41].

14.2.2 Chemotherapy

As stated above, DIPG tumor cells are infiltrative, intertwined with normal cells in the brainstem. They may extend contiguously into the midbrain and medulla, locally into the cerebellar peduncles, and involve the subventricular space and leptomeninges, suggesting that non-focal adjuvant treatment is needed. Despite a number of investigational trials, no therapy except radiation therapy has ever demonstrated any significant anti-tumor effect, clinical benefit, or significant improvement in outcomes in a clinical trial for children with DIPG. Consequently, the standard treatment for children with DIPG has not changed in decades. Many children with DIPG are enrolled in clinical trials; these have investigated various chemotherapeutic

agents and strategies, including conventional cytotoxic agents, high-dose chemotherapy strategies, chemo-radiotherapy, and molecularly targeted agents. Attempts to address the lack of chemotherapy efficacy by varying the timing of chemotherapy administration have been explored, including pre-radiation chemotherapy, chemotherapy concurrently with radiation therapy, and post-radiation chemotherapy. A number of obstacles have been identified as a result of these approaches; despite wide-ranging approaches, DIPG has remained elusive. While subsequent clinical trials have been designed to overcome specific obstacles, the typical drug development and standard clinical trial paradigm has not significantly changed to *collectively* address these obstacles.

14.2.2.1 Empiric Therapies

For years, we had been hampered by the assumption that the biology of DIPG was similar to adult supratentorial malignant glioma as they appear histologically similar. Consequently, chemotherapeutic agents evaluated in clinical trials for children with DIPG have been selected based upon adult malignant glioma data or empirically, as disease-specific pre-clinical tools, such as DIPG cell lines and animal models, were non-existent until relatively recently. The combination of procarbazine, lomustine and vincristine (PCV), a regimen that is modestly active in adult malignant glioma, was one of the earliest therapies explored in children with high-grade glioma, including diffuse intrinsic brainstem glioma [47]. However, the outcome for these patients was not improved. As the PCV regimen was replaced by radiation therapy with concomitant, followed by adjuvant, temozolomide as the standard therapy for adults with glioblastoma multiforme [48], interest in evaluating temozolomide for children with DIPG peaked. Despite its activity in adult glioblastoma, its good central nervous system (CNS) tissue penetration [49], easy accessibility, tolerability, and numerous clinical trials in children with DIPG, *no* clinical trial has demonstrated significant activity of temozolomide in children with DIPG [6, 50–59] (Table 14.1). Accordingly, the multiple trials demonstrating the lack of temozolomide efficacy in DIPG generated suspicion that DIPG may biologically differ from adult glioblastoma and heralded further exploration into DIPG biology.

Administering chemotherapy at different timepoints in the disease course has been evaluated in children with DIPG. In a study evaluating pre-radiation chemotherapy followed by hyperfractionated radiation therapy (total dose was 66 Gy), children with newly diagnosed high risk brainstem tumors were treated with four cycles of cisplatin and cyclophosphamide [61]. Notably, approximately two-thirds of eligible patients (n = 32) clinically improved with steroids and chemotherapy, and radiographic responses were observed with three partial responses. However, the median survival of 9 months was similar to historical controls, and significant chemotherapy-related toxicities were observed.

Table 14.1 Temozolomide studies in diffuse intrinsic pontine glioma (or brainstem glioma, where indicated)

Study Treatment Regimen	Population	Results	Reference
XRT + concurrent TMZ [75 mg/m^2/d] then TMZ [75–100 mg/m^2 daily × 21/28 × 12 courses]	Newly diagnosed DIPG [n = 43]	Median TTP 5.6 mo Median OS 9.5 mo	[59]
XRT + concurrent TMZ [75 mg/m^2/d] then TMZ [200 mg/m^2/d Days 1–5 q 28 d]	Newly diagnosed DIPG [n = 20]	Median PFS 6.9 mo Median OS 9.15 mo	[53]
XRT + concurrent TMZ [75 mg/m^2/d] then TMZ [200 mg/m^2/d Days 1–5 q 28 d × 6 cycles]	Newly diagnosed DIPG [histologically confirmed] [n = 21]	Median TTP 7.5 mo Median OS 11.7 mo	[54]
XRT + TMZ [90 mg/m^2/d] then TMZ [200 mg/m^2/d Days 1–5 q 28 d × 10 cycles]	Newly diagnosed DIPG [n = 63]	Median TTP 6.1 mo Median OS 9.6 mo	[52]
XRT then TMZ [150 mg/m^2/d Days 1–5/28] Or XRT + TMZ [75 mg/m^2/d] then TMZ [150 mg/m^2/d Days 1–5/28]	Newly diagnosed DIPG [n = 18]	Median PFS 7.4 mo [n = 10] Median PFS 6.4 mo [n = 8] Median OS 12.3 mo [all]	[60]
XRT + TMZ [85 mg/m^2/d] × 6 weeks, followed by TMZ [85 mg/m^2/d]	Newly diagnosed diffuse BSG [n = 15]	Median TTP 5.13 mo Median OS 9.8 mo	[57]
XRT + concurrent TMZ [75 mg/m^2/d] then TMZ [200 mg/m^2/d Days 1–5 q 28 d]	Newly diagnosed DIPG [n = 15]	Median PFS 7.15 mo Median OS 15.6 mo	[58]
XRT + TMZ [75 mg/m^2/d] then [200 mg/m^2/d] × 5 with cis-retinoic acid [100 mg/m^2/d] × 21 d/28-d cycle.	Newly diagnosed DIPG [n = 12]	Median TTP 10.2 Median OS 13.5	[50]
TMZ [200 mg/m^2/d × 5 q 28 d]	Progressive diffuse BSG [n = 21]	Median OS 6.2 mo	[55]
XRT [pre-XRT irinotecan, optional] then TMZ [200 mg/m^2/d × 5 d q 28 d × 6 cycles]	Newly diagnosed diffuse BSG [n = 33]	Median PFS ~ 8.5 mo Median OS 12 mo	[56]
TMZ [75 mg/m^2/d × 5 d q 28 d cycle] + O^6-BG	Recurrent, progressive BSG [n = 16]	6-mo PFS = 0% Median OS = 60 days	[51]

Abbreviations: *BSG* brainstem glioma, *d* day(s), *DIPG* diffuse intrinsic pontine glioma, *mo* months, *n* number, *OS* overall survival, *O^6-BG* O^6-Benzylguanine, *PFS* progression-free survival, *q* every, *TMZ* temozolomide, *TTP* time to progression, *XRT* radiation therapy

Pre-radiation chemotherapy with BCNU, tamoxifen, cisplatin and methotrexate was explored in n = 23 children with diffuse brainstem glioma on the BSG 98 trial [62, 63]. Patients on this study had a reported OS of 17 months compared to 9 months in historical controls. While this difference appears significant, the two groups were not prospectively matched. Additionally, children treated with pre-radiation chemotherapy had significantly longer hospital stays compared to the control group. A follow up retrospective review of patients (n = 16) treated as per BSG 98 from 2004–2014 at a single institution was performed and compared these patients to children (n = 9) who underwent stereotactic biopsy for treatment on targeted therapy protocols at the same institution [63]. Median OS was 16.1 versus 8.8 months, respectively. However, again, the groups were not matched by prognostic factors such as length of symptoms, age at diagnosis, biopsy or debulking, or shunt placement. The clinical benefit of this approach, therefore, should be interpreted with caution, and further randomized trials are needed.

14.2.2.2 Disease-Specific Targeted Therapy

The early 2000's ushered molecularly targeted agents into the clinic, and, as with temozolomide, a number of targeted agents were evaluated in clinical trials for children with DIPG (Table 14.2). These trials were frequently performed without knowledge of the target being present or if the "target" was a factor in driving tumorigenesis, as our understanding of DIPG was limited given that biopsy was not routinely performed in the United States, even for research purposes, until later. Targeted agents selected for clinical trials in children with DIPG were primarily those being evaluated in adult glioblastoma patients. While targets, such as epidermal growth factor receptor (EGFR), had been identified in some DIPG cells using tissue obtained at surgical biopsy or autopsy [64], targeted therapies have not improved the outcomes to date. In an initial study of nimotuzumab, a humanized immunoglobulin G-1 (IgG1) monoclonal antibody targeting ERBB1/EGFR, administered with radiation therapy in children with DIPG, median progression-free survival (PFS) and OS were 5.8 months and 9.4 months, respectively [65]. In a follow-up study, Massimino et al. [66] evaluated the efficacy of nimotuzumab with vinorelbine and radiation therapy in children with newly diagnosed DIPG. Unfortunately, median PFS of the 25 eligible patients was 8.5 months. Of note, biopsy to confirm the presence of EGFR expression in the clinical trials was not routinely performed; the authors report one of four biopsied patients demonstrating cytoplasmic membrane expression of EGFR [66]. Additional clinical trials incorporating molecularly targeted agents for children with DIPG are listed, along with outcomes, in Table 14.2. While studies from autopsies of children with DIPG suggest the possible presence of these targets in some patients with DIPG, confirmation of the presence of the target was not performed prospectively for eligibility

Table 14.2 Diffuse intrinsic pontine glioma clinical trials involving molecularly targeted agents

Target(s)	Phase	Study Drug(s)	Confirmation of target present in DIPG required for eligibility? Y/N	Outcomes	Reference
PDGFR	I	Imatinib	N	Median EFS ~7.2 mo Median OS ~11 mo	[67]
VEGFR-2 EGFR	I	Vandetanib + XRT	N	Median PFS ~8 mo Median OS ~11.5 mo	[68]
VEGFR-2 PDGFR	I	Vandetanib + Dasatinib	N	Median OS ~ 12 mo	[69]
EGFR	I	Erlotinib + XRT	Y for newly diagnosed BSG	PFS 8 mo OS 12 mo No correlation of EGFR and OS	[70]
EGFR	I	Gefitinib + XRT	N for BSG	1-year PFS 16.1% 1-year OS 48%	[71]
EGFR	II	Gefitinib + XRT	N	Median PFS 7.4 mo Median OS ~12 mo	[72]
Farnesyl transferase	I	Tipifarnib + XRT	N	Median PFS ~ <6 mo Median OS ~8.5 mo	[73]
Farnesyl transferase	II	Tipifarnib + XRT	N	Median PFS 6.8 mo Median OS 8.3 mo	[74]
Farnesyl transferase	II	Tipifarnib	N	For recurrent, progressive BSG 6-mo PFS 3% +/− 3%	[75]
Gamma secretase	I	MK-0752	N	Refractory BSG [n = 6]: no responses, no long-term stable disease	[76]
Protein kinase C PI3K/Akt pathways	I	Enzastaurin	N	BSG [n = 5]: no objective responses but 2/5 BSG had stable disease >3 cycles	[77]

Abbreviations: *BSG* brainstem glioma, *EFS* event-free survival, *EGFR* epidermal growth factor receptor, *mo* months, *n* number, *N* no, *OS* overall survival, *PDGFR* platelet derived growth factor receptor, *PFS* progression-free survival, *PI3K* phosphatidylinositol-3-kinase, *VEGFR* vascular endothelial growth factor receptor, *XRT* radiation therapy, *Y* yes

in the majority of these studies. Additionally, most targets, including EGFR, identified in DIPG are not found in *all* tumor cells [64], suggesting that additional/combinatorial therapies may be necessary.

Over the past decade, we have learned that there are significant biological differences between adult glioblastoma and DIPG, and even between pediatric supratentorial malignant glioma and DIPG [78]. Subsequently, there has been a rapid expansion in our understanding of the biology of DIPG due to increasingly available autopsy/biopsy tissue and development of DIPG cell lines and animal models.

The availability of this material, paired with the advent of next generation sequencing tools, has enabled groundbreaking research, revealing a complex genomic and epigenetic landscape that characterizes DIPG as a unique disease entity. The recurrent failures of prior clinical trials in DIPG, the identification of potential therapeutic targets from autopsies of children with DIPG, and the safety of routine biopsy of children with DIPG as demonstrated in Europe [79] support performance of biopsy within the context of clinical trials, particularly for confirmation of targets of molecularly targeted agents for children with DIPG [79–84]. However, while clinical trials incorporating biopsy to identify potential targets in individual patients with DIPG have been performed and are ongoing, no improvement in patient outcomes has been reported yet. The lack of efficacy of molecularly targeted agents, as with other chemotherapeutic agents, is likely multifactorial (Table 14.3).

Unfortunately, routine assessment of tumors before and after treatment to confirm target presence and effects of therapy or development of resistance are not routinely or easily performed, especially for DIPG, where repeat patient tumor sampling raises ethical issues, and animal models do not faithfully represent the patient condition. However, continued development and utilization of DIPG disease-specific pre-clinical tools, including cell lines and xenograft models, have allowed the performance of high throughput drug screens and validation of drug activity in animal models. The initial in-depth DIPG-specific drug-screen utilized a panel of sixteen cell lines derived from children with DIPG to evaluate the activity of eighty-three drugs [85]. The histone deacetylase (HDAC) inhibitor, panobinostat, demonstrated significant activity in 12 of 16 cell lines; this activity was validated in an orthotopic xenograft model of DIPG [85]. The demonstration of HDAC activity in DIPG coincided with the identification of histone mutations in up to 80% of children with DIPG [5, 86, 87], providing a rationale for clinical trials of panobinostat in children with progressive [88] and newly diagnosed post-radiation therapy DIPG (NCT02717455).

Table 14.3 Requirements for efficacious molecularly targeted agents for central nervous system tumors

Requirement	Means of Assessment
Active agent(s)	Identify and validate pre-clinically in DIPG cell lines; tumor models
Presence of target	Patient biopsy prior to treatment
Agent delivered to tumor cells	Determine CNS penetration pre-clinically; patient biopsy after drug administration; imaging of drug/metabolites
Effective exposure [adequate concentration over the necessary period of time] at the tumor site	Determine CNS penetration pre-clinically; imaging of drug/metabolites
Patient able to tolerate doses needed to achieve effective exposure	Phase I clinical trial with pharmacokinetic analysis
Lack of resistance mechanisms	Evaluate patient tumor at time of progression/treatment failure

Abbreviations: *CNS* central nervous system, *DIPG* diffuse intrinsic pontine glioma

Most DIPGs harboring histone H3 mutations have distinct genetic partner mutations that may drive tumorigenesis and may be targetable [85, 89, 90]. This is important as resistance to HDAC inhibition develops in DIPG tumor cells [85], suggesting that combinatorial therapy is necessary. Several pre-clinical studies have demonstrated synergistic activity of agents with HDAC inhibitors [91]. For example, combinatorial therapy of HDAC inhibitors with bromodomain containing protein 4 (BRD4) or cyclin dependent kinase 7 (CDK7) inhibition is synergistic against DIPG cells [91]. Other partner mutations, such as *ACVR1,* typically associated with the H3.1K27M mutation, lead to activation of bone morphogenetic protein (BMP) signaling and, ultimately, increases the transcription of tumor growth promoting genes [92–94], suggesting that targeting *ACVR1* concurrently may have an antitumor effect. Pre-clinical studies evaluating combinations of agents are currently underway to validate *in vivo* efficacy to strengthen the rationale for clinical trials in children with DIPG.

14.2.2.3 Biologic Agents

In addition to traditional chemotherapeutic agents, alternate therapeutic approaches, including biologic agents, have been explored. Agents with multiple potential antitumor mechanisms, such as thalidomide and its derivatives, and a variety of interferons have been clinically evaluated for the treatment of malignant gliomas with mixed results [95–101]. Several clinical trials utilizing interferons, a family of glycoproteins with antiproliferative and immunomodulatory effects, have been studied for the treatment of malignant gliomas, but the optimal type of interferon, schedule and dosing remains unclear. Based on a pre-clinical study demonstrating that continuous low-dose interferon alfa may be more efficacious than intermittent high doses [102], Warren et al. performed a Phase II study in children with DIPG, initiating weekly low-dose pegylated interferon alpha-2b (PEG-Intron®) after completion of radiation therapy [101]. Although well-tolerated, median TTP was 7.8 months and OS was 11.7 months, which was not significantly different from historical controls.

Given that malignant gliomas are recognized as vascular tumors with overexpression of basic fibroblast growth factor, vascular endothelial growth factor, and platelet derived growth factor, agents such as thalidomide and its subsequent derivatives, including lenalidomide, have been evaluated in clinical trials for children with brainstem gliomas [100, 103]. In a study of thalidomide with radiation therapy, followed by thalidomide, median TTP was 5 months and median survival was 9 months [100]. In a study evaluating thalidomide and temozolomide with and following radiation therapy in children with diffuse pontine glioma, median PFS was 7.2 months and OS was 12.7 months [103], again, not significantly different from historical controls. Most recently, the thalidomide derivative and immunomodulatory agent, lenalidomide, has been evaluated concurrently and following radiation therapy in a Phase I trial in children with newly diagnosed DIPG [104]. This study

has demonstrated tolerability of lenalidomide in this population and long-term (3+ years) survival of a child with H3.3K27M DIPG; additional outcome results have not been reported to date.

14.2.2.4 Different Modes of Delivery

A major obstacle to optimal anti-tumor effect of chemotherapeutic agents is the blood-brain barrier (BBB), which prevents delivery to, and achievement of, effective exposure to the majority of therapeutics at the tumor site. Because potentially druggable targets have been identified in children with DIPG, and agents designed to target them are available clinically, alternate modes of drug delivery are being explored. These alternative modes of delivery include intrathecal delivery, which is limited by diffusion across the brain parenchyma; intranasal delivery, which continues to be preclinically investigated for optimal drug formulations and validation; and direct intratumoral delivery using techniques such as convection enhanced delivery (CED).

In CED, a therapeutic agent is administered through a catheter, attached to a pump, and infused with low, slow continuous pressure [105]. This technique is being evaluated as a means to improve outcomes for DIPG patients by bypassing the BBB and directly infusing a therapeutic agent into the tumor. The first CED case in a child with DIPG involved the administration of interleukin-13-pseudomonas exotoxin (IL13-PE) directed at the IL13 receptor, which had been shown to be present in a subset of patients with DIPG [106]. While this demonstrated safety and feasibility, this case and the subsequent clinical trial identified, and have sought to rectify, technical issues to optimize delivery to the tumor [107, 108].

Additional studies incorporating different agents have confirmed the relative safety and feasibility of this technique for children with DIPG [109]. Souweidane et al. recently published results of a CED Phase I study in children with DIPG in which the radiolabeled antibody, radioisotope iodine 124 conjugated to antiglioma monoclonal antibody 8H9 ([^{124}I]-8H9), which targets the glioma-associated B7-H3 antigen, was infused [109]. This study again confirmed the safety and feasibility of this technique, and elegantly assessed the volume of distribution of the agent. Development of multiple-catheter, implanted CED devices that allow repeat drug administration to the tumor have also been investigated and shown to be safe and feasible [110, 111]. With each of the direct delivery techniques, drug selection is key; as with all tumors, tumor cells need to be sensitive, and effective exposure at the tumor site needs to be maintained. One of the limitations of CED is complete coverage of the tumor. While CED studies to date have targeted the MRI-defined tumor volume, DIPG tumor cells frequently reside outside the pons [28], likely necessitating the combination of CED and systemic drug administration.

Regardless of type of chemotherapy and route of administration, for chemotherapy to be effective, it has to meet the following minimum criteria: tumor cells must be sensitive to the agent(s); the drug must be delivered to its site of action (i.e. tumor

cells in pons as well as the invasive edge, subventricular zone, etc.); effective exposure (concentration over time) of the active drug or metabolite must be achieved at the tumor site; and patients need to tolerate the doses necessary to achieve these criteria. Unfortunately, pre-clinical studies addressing each of these criteria specifically for DIPG are not routinely performed. Drug penetration into the CNS after systemic delivery is limited for most (>95%) compounds; only small, lipophilic compounds are able to cross the BBB and then must traverse the brain parenchyma to reach the tumor cells [112]. Until each and all of these requirements are addressed, the likelihood of identifying effective chemotherapeutic agents for DIPG remains minute.

14.3 Treatment of Pediatric Non-DIPG Brainstem Gliomas

Questions that commonly arise for benign or low-grade appearing lesions on MRI, particularly in patients who are asymptomatic, minimally symptomatic, or have associated neurofibromatosis type I (NF-I) are: (1) is there a need for biopsy, (2) when to institute treatment, and (3) what treatment is recommended. Focal and dorsal exophytic brainstem gliomas and cervicomedullary gliomas are most commonly low-grade lesions. These patients may have a surgical option depending on tumor size and tumor location [10, 12]; safe, maximal surgical resection is the initial treatment of choice [113]. For most cases, obtaining tumor tissue for histologic diagnosis is optimal if the lesion is accessible, particularly if the lesion is rapidly increasing in size. Enhancement patterns alone in pediatric brainstem gliomas are not used as diagnostic criteria or a rationale for biopsy. In adults, malignant gliomas typically enhance, while low-grade gliomas are less likely to enhance, therefore in adults, enhancement on MRI may be an indication for biopsy. In contrast, in pediatric brainstem gliomas, diffuse malignant lesions such as DIPG may not enhance or have minimal enhancement, while non-DIPG tumors, which are frequently pilocytic astrocytomas, often do enhance [17, 114].

For asymptomatic patients and patients who undergo subtotal/incomplete resection, conservative management with a period of watchful waiting and close monitoring may be appropriate [113, 115].

In patients with NF-I, non-enhancing enlarging lesions in the brainstem are sometimes presumed to be low-grade gliomas and treated as such. In a retrospective study of brainstem tumors in children with NF-1 and brainstem tumors, 12 of 21 patients had progression of the lesion in a 3.75 year follow-up, and in 7 patients, the lesion stabilized or regressed without intervention [116], suggesting that a conservative approach of watchful waiting/observation is appropriate.

The optimal timing for initiating non-surgical treatment for non-DIPG brainstem gliomas in children is not clear. In general, if a lesion is causing symptoms and/or there is evidence of progression, treatment is instituted. Surgical resection may be performed at diagnosis in lesions that are readily accessible surgically. If debulking or partial resection is performed and the lesion is found to be a pilocytic astrocytoma, sometimes watchful waiting is done as the residual lesion may spontaneously

regress [117]. If there is evidence of tumor growth or worsening tumor-associated symptoms, the recommended treatment takes into consideration the patient age, evidence of malignancy, rapidity of growth, risk of loss of function, and presence of targetable mutations.

14.3.1 Radiation Therapy

Radiation therapy can be utilized for unresectable or incompletely resected lesions, rapidly progressing lesions, or disease progression after chemotherapy [1, 118, 119]. In a retrospective analysis of children with focal brainstem lesions, tumor control after surgery or radiation therapy were comparable [10]. However, the risk of radiation-induced toxicities, including long-term toxicities such as secondary malignancy, must be taken into consideration given that the vast majority of children with non-DIPG brainstem tumors will survive and effective chemotherapeutic regimens exist [120, 121]. When radiation therapy is indicated, focal tumor volumes are generally used to decrease the potential for acute and long-term toxicities [113].

Cervicomedullary tumors are also frequently low-grade gliomas including pilocytic astrocytomas, fibrillary astrocytomas, and gangliogliomas [11, 114, 122]. Despite their diffuse appearance, safe surgical resection is generally the treatment of choice. However, this is not possible in a number of cases; subtotal resection may be feasible and is frequently followed by radiation therapy [11]. Robertson et al. reported a 70% PFS rate in 17 children with histologically low-grade cervicomedullary tumors (n = 15) or anaplastic gangliogliomas (n = 2) that were treated with surgical resection alone. Again, watchful waiting/close observation may be appropriate. If tumor size or symptoms are rapidly progressive or there is impending loss of function, radiation therapy may be indicated. If there is slow progression, chemotherapy may be an option, particularly if BRAF V600E mutations are present [123, 124]. OS is significantly better than diffuse tumors involving the pons, with over 80% 5-year survival [11].

14.3.2 Chemotherapy

There is no standard of care for the use of chemotherapy in the treatment of pediatric non-DIPG brainstem gliomas. Rather, standard chemotherapeutic regimens utilized for children with low-grade gliomas in other locations are frequently employed. Chemotherapy is often recommended for patients with unresectable tumors, those with residual tumor following surgical resection, and those with progressive or symptomatic lesions. One report advocated pre-surgery chemotherapy as a means to improve the brainstem/tumor interface of cervicomedullary gliomas to allow for more successful resection [122]. However, specific chemotherapy regimens have not been prospectively evaluated in clinical trials in this population.

Historically, several cytotoxic chemotherapy regimens, such as vincristine and carboplatin [125], 6-thioguanine, procarbazine, lomustine and vincristine (TPCV) regimen [126], and vinblastine [127], have been used with some success in the management of children with low-grade gliomas, including those involving the brainstem [128]. Recent advances in our understanding of glioma biology and identification of potential targets, such as BRAF in low-grade gliomas and gangliogliomas, have led to more directed treatment. For example, the BRAF-KIAA1549 fusion is found in approximately two-thirds of brainstem pilocytic astrocytomas [129, 130] and BRAF V600E is frequent in gangliogliomas, found in more than 50% of pediatric patients [131, 132].

14.4 Treatment of Adult Brainstem Gliomas

As discussed, the incidence of adult brainstem gliomas is relatively low as the vast majority of malignant gliomas in adults are supratentorial. As a result, treatment for adult brainstem glioma is not standardized but rather based upon provider/institution experience and individual patient factors. Over the past decade, a limited number of retrospective studies have been performed to assess and characterize the clinical management of this patient population. These studies involve heterogeneous populations, relatively small patient numbers, and varied treatment approaches, including radiation therapy, chemoradiation therapy, chemotherapy alone, surgery only, or watchful waiting [133–136]. While pediatric brainstem tumors are typically characterized as DIPG versus non-DIPG, a functional approach for the classification of adult brainstem gliomas appears to more commonly be high-grade (WHO III/IV) versus low-grade (WHO I/II) gliomas, as this seems to have the strongest prognostic implications [133]. Therefore, stereotactic biopsy has been suggested as the standard of care in adult brainstem gliomas [13, 133, 137], particularly given the fact that, unlike in pediatrics, a considerable proportion of adult brainstem lesions are not gliomas [4, 137]. Additionally, some adult brainstem gliomas may be described as focal, dorsally exophytic or cervicomedullary lesions [12] as in the pediatric population, and these may be amenable to surgical resection as discussed above.

14.4.1 Radiation Therapy

Radiation therapy is commonly employed for adults with brainstem glioma [4, 134], particularly those that are high-grade or unresectable, progressive lesions [136], although the indication for radiation therapy is not defined in many cases. Most patients do have improvement in clinical symptoms after radiation therapy,

although the impact on survival is not clear [138]. As with other malignant gliomas, radiation doses of 50–60 Gy administered via focal fractionated external beam irradiation is commonly utilized [133, 139].

14.4.2 Chemotherapy

The role of chemotherapy in the treatment of adult brainstem gliomas has not been established [135], and only few studies have evaluated chemotherapy specifically in this population. A retrospective analysis of 28 patients that compared OS for adults with brainstem glioma treated with radiation and concurrent temozolomide, followed by temozolomide, versus those receiving radiation alone did demonstrate a survival advantage (23.1 vs. 4.0 months) [16], and several retrospective analyses indicate that temozolomide, alone or concurrently with radiation therapy, is frequently employed for adults with brainstem glioma [135]. However, the clinical benefit from chemotherapy, including temozolomide, is unclear as randomized prospective trials comparing similar populations have not been performed.

Other chemotherapeutic agents commonly used in adult supratentorial malignant glioma have been employed at the time of recurrence/progression of brainstem glioma. These therapies include bevacizumab, nitrosoureas, PCV regimen, and platinum compounds, among others [135]. As with upfront chemotherapy, their role is unclear as patient numbers are small, tumors are heterogeneous, and these have not been evaluated in clinical trials [135].

14.5 Treatment at Relapse

Unfortunately, the vast majority of patients with malignant glioma involving the brainstem will progress after upfront therapy. Treatment options at this time are limited, and many patients opt for clinical trials or palliative care. Frequently, patients are ineligible for clinical trials given their poor performance status, short life expectancy [140], or exclusion of patients with tumors located in the brainstem. A number of institutions are revisiting the idea of re-irradiation in this patient population. With advanced radiation therapy and imaging techniques, re-irradiation in patients with progressive malignant brainstem glioma has been shown to be feasible and relatively safe, with possible modest efficacy; however, re-irradiation is not standardized, the optimal dose, technique, fraction and volume are unknown, ideal patient selection is unclear, and management of toxicities is necessary. Re-irradiation has resulted in mixed results including improved symptoms and modest survival improvements (median survival 2–9 months) [66, 141–144].

14.6 Conclusion

Brainstem gliomas are a heterogeneous group of tumors that span histologic grades and age groups. The treatment of adults and children with brainstem glioma varies, depending on the radiographic appearance, patient age, tumor type, and tumor biology. Tumor biology is age- and location-dependent. While low-grade gliomas in the brainstem may have surgical and chemotherapeutic options, the treatment of malignant brainstem gliomas is limited to radiation therapy and investigational chemotherapeutic regimens. Unfortunately, the outcome for patients with diffuse brainstem glioma remains poor. Our understanding of DIPG in particular has advanced dramatically over the past decade, yet clinical advances to improve outcomes have been stalled due to obstacles with identifying and delivering effective agents to the tumor site. As we identify tumor targets and molecularly targeted agents and validate these in pre-clinical disease-specific models, we must now focus on overcoming the obstacles of drug delivery and drug resistance. Despite all the limitations, the hope is that a deeper understanding of the microenvironment, tumor biology and brainstem development will soon lead to effective treatments that will improve outcomes for our patients.

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