Diffuse intrinsic pontine glioma: time for therapeutic optimism

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Practice points

- Diffuse intrinsic pontine glioma (DIPG) is the most lethal tumor of the CNS in children. No curative therapies are available and the median survival has been less than 1 year over the last two decades. The biology of this tumor remains elusive though recent insights to its oncogenesis are now deciphering.
- Paradigm shift in performing up-front biopsy have helped in identifying the cellular origin and key molecular drivers of this tumor formation, and this trend is increasingly pursued.
- Molecular subtypes are now identified, which includes a hypoxia-driven mesenchymal phenotype and a proneural/oligodendroglial differentiated phenotype associated with PDGFRA amplification. Also mRNA evaluation indicates two different subgroups based on the Myc or Sonic Hedgehog (Shh) signaling. It is now clear that DIPG biologically differs from other high-grade gliomas in adults and other parts of the CNS in children. All these newer perspicacity needs to be considered as the next generation biologically driven trials are being profiled.
- Targeting major biomarkers which include histone modulators and key molecules of the PI3/Akt pathway should be incorporated in future clinical trials.
- The next decade should prioritize endeavors to improvise locoregional delivery techniques of newer biologic agents and immunotherapeutic strategies.
- Ahead lays the task and challenge in the ability to comprehensively evaluate all the fast-accumulating knowledge of molecular biomarkers and subtypes in DIPG, and be able to identify optimal effective DIPG-specific trials.

SUMMARY Diffuse intrinsic pontine glioma (DIPG) is an aggressive tumor that is universally fatal, and to-date we are at a virtual standstill in improving its grim prognosis. Dearth of tissue due to rarity of biopsy has precluded understanding the elusive biology and frustration continues in reproducing faithful animal models for translational research. Furthermore the intricate anatomy of the pons has forestalled locoregional therapy and drug penetration. Over the last few years, biopsy-driven targeted therapy, development of *vitro* and xenograft animal models for therapeutic testing, profiling immunotherapeutic strategies and locoregional infusion of drugs in brain stem tumors, now provide a sense of hope in the years ahead. This review aims to discuss current status and advances in the management of these tumors.

KEYWORDS

- oncogenic drivers
- pontine glioma • signaling pathways • targeted therapy
- tumor heterogeneity

Diffuse intrinsic pontine glioma (DIPG) comprise 70–80% of brain stem tumors in children with an annual incidence of nearly 300 in the USA. Despite the collaborative efforts and the advancement in the multimodality management of brain tumors, the prognosis of these tumors has remained dismal over the last two decades and pose therapeutic challenges. The median overall survival (OS) has

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remained 9–12 months [1,2]. These tumors occur commonly between the ages of 5–10 years, arising from the pons causing its diffuse enlargement. The onset of symptoms from presentation is usually short with a median of 1 month [3]. Classical presentation includes a triad of neurologic signs, which include involvement of long-tract (extremity weakness and hyper-reflexia), multiple cranial nerve deficits, usually the sixth or seventh nerve, and cerebellar involvement with ataxia and or incoordination [4]. Tumor progression is usually local though leptomeningeal dissemination has been reported in 4–39% of cases, questioning the need for surveillance with craniospinal imaging [5]. Radiation therapy is the only therapeutic modality that has consistently shown clinical and radiographic responses in these children. Nearly 70% of children improve neurologically following radiotherapy and objective responses are seen in 30–70% of children, although are short-lived [6]. The diagnosis of these tumors is usually made by neuroimaging alone, which has specific characteristics. Brain MRI is usually diagnostic, which show a large expansile, pontine-based lesion often extending rostrally into the midbrain or caudally into the medulla and cerebellar peduncles. These tumors are relatively hypo- or iso-intense on T1 and hyperintense on T2-weighted images compared with the normal brain [7,8]. Contrast enhancement pattern is usually heterogeneous. Although these tumors are diagnosed based on classic MRI findings and avoidance of biopsy still remains the consensus, other pathological entities like primitive neuroectodermal tumors and gangliogliomas may have intrinsic pontine locations and can be diagnostically confusing. Thus atypical neuroimaging of pontine lesions should warrant a biopsy to confirm the pathology (Figure 1). DIPG are generally diffuse fibrillary astrocytomas at diagnosis but can range from grade II–IV as per the WHO classification. However at autopsy, most tumors are found to be high-grade gliomas (HGG) [9]. Over the last three decades as newer therapies continue to be evolve, a paradigm shift in diagnostic modalities have moved along in parallel. Till the 1990, CT scan was most widely used for diagnosis and treatment follow-up. With the advent of MRI better delineation of the brain stem is possible. Ongoing refinement of advanced neuroimaging techniques continue, to better define tumor characteristics and understand the metabolic and anatomic profile of DIPG using magnetic

resonance spectroscopy (MRS) and perfusion imaging modalities. In addition, evaluation of fiber track changes using diffusion tensor imaging (DTI) and fractional anisotropy (FA) are now performed with better precision. Since the last few years, in addition to the evolving newer neuroimaging techniques, use of upfront biopsy are now being performed in various institutions to understand the molecular signature of these tumors and define targeted therapeutic approach. However, even though multiple chemotherapeutic regimens, newer biological therapy, varying schedules of radiation treatment and combination therapies have been used, this has not translated into a meaningful survival benefit [10]. Recent development of brainstem tumor models, early reports of success in convection-enhanced delivery (CED) of biological agents into the brain stem, increased identification of signaling pathways and oncogenic drivers have triggered enthusiasm and hope.

Is it time to biopsy again?

Stereotactic biopsy of these tumors became popular after the first report of this procedure in 1978 [11]. Since the mid-1980s, the argument against biopsy became stronger as this was thought to have poor yield and biology of the limited sample would not be truly representative of the entire tumor [12]. Thus treatment strategies were developed in children, based on clinical trials which showed encouraging responses in adults with HGG that unfortunately did not translate into increased OS. This clearly undermined the assumption that DIPG can be treated similar to adults with HGG and biopsy is not warranted [13]. The last decade has seen growing evidence that biopsy is not only safe but diagnostically accurate. A total of 44 children with diffuse brain stem lesions on MRI scans underwent biopsy, which showed 10% having a pathological diagnosis different from glioma [14]. Cumulative experience from over 300 children who underwent biopsy for pontine tumors showed that postoperative symptoms and signs are relatively infrequent and majority of these consisted of transient cranial neuropathies or mild motor weakness [15,16]. Increasing use of DTI, tractography and PET ‘hotspots’ to locate the corticospinal tracts during surgical evaluation, have resulted in lowering of morbidity and re-defining safety of biopsy [17,18]. Two recent studies on 99 children demonstrated feasibility of stereotactic biopsy in pontine tumors using

Figure 1. MRI of classical and atypical diffuse intrinsic pontine glioma. (A & B) Show diffuse bright signal on axial FLAIR with encasement of the basilar artery and heterogeneous enhancement on sagittal T-1 postcontrast. **(C & D)** Show atypical features of involvement of the pons in a case of ganglioglioma on axial T2 and sagittal T-1 postcontrast.

intraoperative neuronavigation techniques with high diagnostic yield [19,20]. The quality and quantity of the material obtained was also adequate for an extended molecular screening and biomarker study. Thus there is a global resurgence of performing upfront biopsy in DIPG patients for molecular profiling, to drive the next generation of biologically directed therapy, based on individualized tumor biomarker phenotype.

Update on cellular origin & experimental models

Gliomas arising from the ventral region of the pons are usually diffusely infiltrative and can range from WHO (grade II–IV). Lack of faithful reproducible experimental models has limited understanding and defining the neural precursor cell leading to formation of DIPG. Newer insights now reveal a unique type of nestin and vimentin immunopositive cell population in the

developing postnatal human brain to be present in the ventral pons. Also of interest is that nearly half of these cells are positive for the transcription factor olig2. The increased presence of these cells (nestin + vimentin + olig2 +) are noted in middle childhood when the incidence of DIPG peaks. Thus these cells are likely linked anatomically and temporally to the incidence of DIPG and could be a cell of origin for this tumor formation. Upregulation of the *Shh* pathway and Hedgehog-responsive cells is seen to develop in the ventral pons of mouse models corresponding to the time when the incidence of DIPG surges. The role of this pathway in the oncogenesis of DIPG is further substantiated by the positive effects of self-renewal on DIPG neurosphere cells in culture models. The authors also suggest that the ‘candidate cell of origin for DIPG’ gives rise to oligodendrocyte precursor cell type that expresses PDGF. Addition of recombinant

PDGF to human DIPG cell culture resulted in improved culture yield [21]. In newly diagnosed children with DIPG, upregulated genes known to be involved in the *Shh* pathway were also seen in contrast to the HGG tumors in children. Additionally, a biological DIPG subgroup with an oligodendroglial phenotype was identified, and seen to be associated with *PDGFRA* gain and amplification [22]. All of these led credence to the role of PDGF in DIPG tumor genesis.

Initial efforts to develop brain stem glioma (BSG) models were initiated in rat models (allograft models) derived from rat cortical gliomas after stereotactic implantation into the brain stem. However, the accuracy of these models to replicate the histology and the genetic phenotype as seen in human tumors remain debatable [23,24]. Recent development of genetically engineered mouse model of BSG using the RCAS/tv-s system provides more insight into the make-up of DIPG including similarity to the histology and pattern of invasion as seen in these human tumors. Encouraging is the recent revelation of the use of experimental orthotopic xenograft mouse models of DIPG and its successful implementation in developing preclinical trials and new agents testing, which fosters hope in profiling effective therapeutics against DIPG [25,26].

Clinical trials & the outcome

Since 1984 to 2005 an extensive review on DIPG revealed 29 studies performed on 973 patients. These trials used conventional, hypo- or hyperfractionated radiotherapy with or without concurrent chemotherapy, different neoadjuvant or adjuvant chemotherapeutic regimens and high-dose chemotherapy with stem cell rescue [27–35]. A study on 23 patients receiving preradiation chemotherapy showed significant improvement of median survival to 17 months compared with historical controls, but increased infection rate and prolonged hospitalizations were a concern to pursue further prospective clinical trials using this regimen [36]. The HIT-GBM-C study using intensive chemotherapy during and after radiation in pontine tumors, showed a marginal improvement in the median survival of these tumors though OS rates did not differ from the control group [37]. However to date no treatment has provided a significant better outcome and OS ranges from 8 to 11 months. Even today focal radiation therapy given over 6 weeks remains the standard of care for newly diagnosed

DIPG. Recent trials suggest that patients with newly diagnosed DIPG given a hypofractionated regimen over 3–4 weeks, offer equal survival with less treatment burden compared with a conventional regimen of 6 weeks [38,39]. With the continued increase in the understanding of the molecular biology of DIPG, focus on target-driven therapy for this tumor has now evolved over the past few years. More signaling pathways and molecular targets continue to be identified leading to important conclusions that pediatric DIPG differs from adult HGG and genomic differences are noted between DIPG and pediatric HGG. From 2005 till 2012, 26 prospective clinical trials in 561 children with newly diagnosed DIPG were published. These included the use of radiosensitizers, targeted therapy using drugs such as imatinib, gefitinib, vandetanib and erlonitib [40–44]. EGF receptor (EGFR) inhibition with monoclonal antibody nimotuzumab was studied. Although the initial results were encouraging, subsequent studies showed only a subset of patients with DIPG appear to benefit from this drug [45,46]. Combined therapy targeting oncogenic drivers at different levels of signaling pathways have been tried using bevacizumab alone or with irinotecan or valproic acid [47,48]. The first ongoing biopsy driven molecular-based trial is open in which radiation is given concurrently with temozolomide, bevacizumab or erlonitib based on the MGMT status, VEGF or EGFR expression of the tumor, respectively [49]. **Table 1** illustrates clinical trials and their treatment response using different therapeutic modalities. Even with these newer trials therapeutic frustrations remains as the median OS continue to range from 4 to 17 months. Due to the recent shift in the paradigm to obtain upfront biopsy, biological data continues to unravel, resulting in the sustained pursuance of exploring molecularly driven targeted therapies.

Drug delivery into pontine tumors

The blood–brain barrier (BBB) effectively protects the brain but poses a major challenge in adequate drug delivery. This is due to the unique intricacy of the BBB, which comprises of a layer of endothelial cells, the capillary basement membrane, pericytes, astrocytes end-feet tightly surrounded by capillaries, forming a sheath [53]. This complex structure hinders drug penetration into the CNS, and often less than 1% of systemically administered drugs reach the tumor area [54]. Over the last several years, research strategies

Table 1. Treatment response and outcome of published studies in diffuse intrinsic pontine glioma patients.

Study	Treatment (%)		Response (%)			PFS (months)	OS (months)	1-year survival (%)	Therapy	Ref.
	CR	PR	MR	SD	PD					
Radiation alone										
Janssens <i>et al.</i>						5	8.5	NA	Hypofractionated	[27]
Mandell <i>et al.</i>	2	31		44	23	6	8.5	31	Hyperfractionated	[28]
Mandell <i>et al.</i>	2	29		45	24	5	8	27	Standard XRT	[28]
Pre-XRT chemotherapy										
Massimino <i>et al.</i>						5	9 [†]	29	Cisplatin, eoposide, <i>cis</i> -retinoic acid	[31]
Frappaz <i>et al.</i>						NA	17 [†]	65	Cisplatin, HDM TX, tamoxifen, carmustine	[36]
Jennings <i>et al.</i>	0	17	12	22	49	NA	NA	30	Carboplatin, cisplatin, vincristine, cyclophosphamide, etoposide	[30]
HDC with XRT										
Dunkle <i>et al.</i>							11 [†]	50	BCNU, thiotipa, etoposide	[35]
Massimino <i>et al.</i>						10	13 [†]	70	Multiple drugs including HDC	[31]
Chemo-radiotherapy										
Cohen <i>et al.</i>		31	21	34	14	6.1	9.6 [†]	40	Temozolomide	[33]
Packer <i>et al.</i>		17	17	58	8	NA	11 [†]	45	RMP-7 and carboplatin	[32]
Wolff <i>et al.</i>	3	22		46	30	4.8	13.6	55	Cisplatin, vincristine, etoposide, ifosfamide	[37]
Post-XRT chemotherapy										
Massimino <i>et al.</i>		26		67	7	NA	9 [†]	27	Etoposide, ara-C, ifosfamide, cisplatin, dactinomycin	[31]
Bouffet <i>et al.</i>						4	10	NA	Thiotepa and busulfan	[34]
Radiosensitizer										
Bradley <i>et al.</i>						NA	7 [†]	NA	Motexafin gadolinium + XRT	[41]
Bernier <i>et al.</i>		40				NA	8.3	25	Topotecan + XRT	[40]
Targeted therapy										
Georger <i>et al.</i>		17		50	33	8	12 [†]	50	Erlotinib + XRT	[50]
Pollack <i>et al.</i>		6				NA	11	45	Imatinib + XRT	[42]
Broniscer <i>et al.</i>						NA	NA	38	Vandetanib + XRT	[44]
Immunotherapy										
Pollack <i>et al.</i>	4	12.50	4	67	12.50	NA	NA		Peptide vaccine, ongoing pilot trial	[51]
Convection-enhanced delivery										
Luther <i>et al.</i>						NA	NA		¹²⁴ I-8H9 CED in DIPG, feasibility study	[52]

[†]Median value.

Ara-C: Cytosine arabinoside; BCNU: Carmustine; CED: Convection-enhanced delivery; CR: Complete response; CT: Chemotherapy; CXRT: Chemo-radiotherapy; DIPG: Diffuse intrinsic pontine glioma; HDC: High-dose chemotherapy with autologous stem cell rescue; HDM: High-dose methotrexate; MR: Minor response; NA: Not available; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; RS: Radiosensitizer; SD: Stable disease; Tx: Treatment; XRT: Irradiation.

have focused on improving the BBB penetration of chemotherapeutic and biologic agents into the tumor area. Feasibility of osmotic BBB disruption using intra-arterial chemotherapy feasibility in DIPG was seen in eight patients, although the response was modest [55]. Lohradimil (a synthetic bradykinin analog), which transiently increases the BBB permeability used with carboplatin showed tolerance of this regimen, but was found to be inactive in these tumors [56].

More recently, CED has been used to deliver agents into the tumors and surrounding space under continuous low-pressure through stereotactically placed catheters in the tumors. This technique has demonstrated safety in several clinical trials of adult patients. Recently infusion of antiglioma cytotoxin IL-13PE directly into a girl with recurrent DIPG demonstrated safety but no survival benefit was noted [57–59]. A recent study showed feasibility of delivering

topotecan by prolonged CED into the brain stem in children with DIPG, although it did not prolong survival [60]. Newer delivery modalities for enhancing drug penetration into the CNS include the biological approaches using nanoparticles and cell-penetrating peptides needs to be explored in these tumors [61].

Evolving molecular era of DIPG

The paradigm shift in the trend to do up-front biopsy of DIPG and the recent consensus at the DIPG Think Tank Consortium that autopsy materials yield high quality DNA suitable for genome-wide studies, has led to increased unravelling of molecular markers. It is now imperative to better understand the genetic signature of this tumor to facilitate profiling optimal therapy.

The first major molecular study looking into 18 surgical biopsies and ten post-mortem specimens of DIPG showed significant expression of *ERBB1* and *ERBB1* gene amplification. No clinical correlation was observed between abnormalities of *TP53*, tumor grade, amplification and/or overexpression of *ERBB1* [62]. Since then, a flurry of genomic studies looking into the genetic/transcriptional signature of this tumor has continued. Focal amplification of nearly 50% of genes within the major pathway of the RTK–Ras–PI3K signaling pathway was demonstrated in a genome-wide analysis of 43 DIPG samples. They included the *PDGFRA*, *MET*, *IGF1R*, and *ERBB4*. This study also showed that significant differences exist in genes that encode transcription factors between DIPG and other HGG of the brain stem [63]. A comprehensive high-resolution genomic analysis of 11 DIPG patient samples showed 30% having gains in the *PDGFRα* and all showed *PDGFRα* expression. Also of interest was the dissimilitude of copy number alteration between DIPG and pediatric supratentorial HGG [64]. These suggest that DIPG differ in their biological phenotype from other HGG of the brain stem and supratentorial tumors in children. Using comparative genomic hybridization multiple chromosomal rearrangements was seen in regions of known oncogenes including *PDGFRA*, *EGFR*, *IRS2*, *MDM4* and *MYCN*. This study reaffirmed that the PI3K pathway could be a major oncogenic route for this tumor formation [65]. Another study identified and reaffirmed oncogenic mutations in the PI3K pathway as major drivers of DIPG tumorigenesis [66].

There has been a recent explosion of studies implicating the role of epigenetic histone

modulators in the pathogenesis and maintenance of brain tumors. Since the first report on the role of histone mutation in pediatric brain tumors in 2012, ongoing studies now demonstrate its role in DIPG [67]. A total of 42 DIPG samples were tested for *H3.3* mutations in the wild-type versus mutated subgroups comparing the incidence of *TP53* mutations and clinical outcome. No difference in the incidence of *TP53* mutations (nearly 75%) were noted between the two subtypes, however, the histone H3.3 wild-type status was associated with better clinical outcome [68]. Whole-genome sequencing of DNA on seven and targeted sequencing on another 43 DIPG samples showed 78% of DIPGs having mutation in the *H3F3A*, which encodes *H3.3* or in the related *HIST1H3B*, encoding histone *H3.1* [69]. Identification in DIPG of a membrane protein B7-H3 known to drive cancers, through its interaction with host defense mechanism was noted both by immunohistochemistry and gene expression, suggesting its role as a potential therapeutic target [70]. Although the role of histone modifiers have been extensively studied and reported, its use in clinical trials have yet to bring about a therapeutic success. Whole-exome and/or transcriptome sequencing in 57 DIPG samples identified recurrent somatic mutations in *ACVR1* and recurrent fusions involving the neurotrophin receptor genes (*NTRK1*, *NTRK2* and *NTRK3*) in 32 and 47%, respectively [71].

Recent preclinical trials have revealed newer insights into cell-cycle regulatory genes leading to aberrant cell proliferation in DIPG. WEE1 kinase, a major gate-keeper of the G₂ cell-cycle checkpoint was noted to be a potential therapeutic target for radiosensitization of adult gliomas and other cancers [72,73]. Marked overexpression of WEE1 kinase was seen in DIPG tissues and tumor tissue, which extends beyond the brain stem. MK-1775 an inhibitor of WEE1 kinase showed reduced G₂-M arrest and decreased viability of DIPG cells and also enhanced radiation response of E98-Fluc-mCherry DIPG mouse xenografts [74]. Alterations in cell-cycle regulatory genes including amplification of D-type cyclins and CDK4/6, or loss of *Ink4a-ARF* is noted in nearly 30% of DIPG tumors. Use of PD-0332991 (PD), a CDK4/6 inhibitor induced cell-cycle arrest in PDGF-B driven BSG mouse model [75]. These studies provide rationality of exploring WEE1 kinase inhibitors with concurrent radiotherapy and CDK4/6 inhibitors in DIPG.

Tumoral heterogeneity/subgroups of DIPG

It is becoming evident that DIPG arise from different oncogenic pathways and are biologically heterogeneous from other gliomas and brain stem tumors and exhibit intertumoral heterogeneity. Based on the differential gene expression analysis, these tumors are now seen to be comprised of two biological subgroups. Type 1 was identified by its overexpression of oligodendroglial markers and marked enrichment of genes known to describe the PDGFRA-amplified and proneural glioma signatures. Type 2 was noted to have significant upregulation of a mesenchymal gene expression signature. This phenotype showed overexpression of many proangiogenic genes and oncogenesis of this subgroup is linked with a hypoxia-induced angiogenic switch, induced by the activation of the HIF1A pathway. This subtype showed significant overexpression of numerous stem cell markers as stated earlier [22]. A recent study using whole-genome sequencing with methylation, expression and copy number analysis in DIPG samples identified three molecularly distinct subgroups, which include silent, MYCN and the H-3-K27M subtypes. The former two groups did not show any *RTK* gene amplification suggesting that targeting this pathway might not be clinically effective in all DIPG. The H-3-K27M subtype were highly mutated in either the histone H3.3 (*H3F3A*) or H3.1 (*HIST1H3B* and *HIST1H3C*) and showed gains or amplifications of *PVT1*, *MYC* or *PDGFRA* and enriched with *TP53* mutations. The intricacy of these subtypes suggests that this group might not benefit with a histone deacetylase inhibitor alone, but could need targeting other molecular markers for better efficacy [76]. Evaluation of protein and mRNA expression profile in 14 DIPG samples showed differential expression of upstream regulatory molecules. They are *Myc* oncogene and the glioma-associated oncogene (*GLI1*), a member of the *Shh* signaling pathway. A global hypomethylation of these tumors was also noted. Thus likely these changes in the DNA methylation may contribute to the *Myc* and *Shh* subgroup genesis and poor response to the use of temozolomide. These recent insights could create therapeutic challenges as focal biopsy-driven molecular diagnosis to guide individualized therapy is now pursued [77]. Sustained flurry of newer revelations into the insights of biological markers and key drivers of DIPG oncogenesis continues. **Table 2** illustrates important molecular markers and their aberrations identified in these

tumors. Although these might provide a sense of optimism, the true challenge lies in the ability to comprehensively evaluate all these data, define major oncogenic drivers of these heterogeneous tumors and be able to optimally profile the next-generation clinical trials.

Role of immunotherapy

Immunotherapy has recently gained increasing attention as a more targeted and less toxic approach for treating brain tumors. With the role of chemotherapy and radiation therapy now at a point of diminishing returns in aggressive brain tumors such as DIPG, different immunotherapeutic methodologies continue to be explored. These include radioisotope-conjugated passive antibodies, peptide based vaccines and dendritic cell-based vaccines [78]. Use of dendritic cell-based vaccine in pediatric gliomas showed some clinical benefit and demonstrated feasibility [79]. Preliminary results in pediatric astrocytoma glioma associated antigen peptide-based vaccination trial showed safety and prolonged response in one child with DIPG [51]. A trial using radioactive substance ^{124}I bound to an 8H9 antibody infused into the brain stem of DIPG patients using CED technique, is currently enrolling patients [52]. Intracerebral injection of human, EGFRvIII-specific, third-generation chimeric-associated receptor-transduced T cells in gliomas of mice, showed promise of its likely use in treatment of brain tumors including DIPG [80]. Judicious use of these immunotherapeutic strategies needs to be explored including the use of CED to introduce CAR- transduced T cells bound with specific antibody against antigens expressed in DIPG. A recent study using cross-tumor comparative analysis demonstrates that different pediatric brain tumor types exhibit distinct immunophenotypes, and thus specific immunotherapeutic approaches may be most effective for each tumor type including DIPG. Although this is interesting it poses challenge in the endeavor's to implement universal immunotherapeutic approaches in brain tumors [81].

Neuroimaging in DIPG: challenges & advances

Most studies have shown poor correlation between conventional MRI appearance and the clinical outcome [82,83]. There are no well-defined enhancement patterns of this tumor precluding drawing conclusions based on this, although a large study demonstrated worse outcomes with

Table 2. Key oncogenic drivers and molecular markers in diffuse intrinsic pontine glioma†.

Molecular markers	Aberration	Frequency (%)	Ref.
<i>ERBB1</i>	Expression/amplification	90	[62]
PI3K pathway activation	Focal amplification	15–45	[63,64]
RB phosphorylation	Amplification	30	
<i>MET, IGF1R</i>	Focal gains	30	
<i>PDGFRA</i>	Gains	36	[64]
	Expression	100	
<i>PARP1</i>	Low-level gains	27	
<i>K27M-H3.3</i>	Mutation	71	[68]
<i>TP53</i>	Mutation	40–77	[63,66]
PDGFRA (with <i>K27M-H3.3</i> mutation)	Gain or amplification	40	
Cell cycle regulatory genes			
RB signaling (<i>CDK4, CDK6, CCND 1, 2, 3</i>)	Gain or amplification	33	[63,66]
<i>WEE1</i>	Overexpression	80	[69]
<i>ACVR1</i>	Recurrent somatic mutations	20–32	[71,76]
Neurotrophin genes (<i>NTRK1, NTRK2, NTRK 3</i>); key oncogenic drivers of DIPG	Recurrent fusions	47	[69]

†RTK–PI3K–Akt pathway; genes regulating the G_i check-point: *TP53, MDM2, CDK* and *ATM*; mutations of histone modifiers and chromatin remodeling.
DIPG: Diffuse intrinsic pontine glioma.

enhancing tumors [84]. Use of advanced MRI techniques such as MRS, DTI to derive apparent diffusion coefficient (ADC) and FA maps now complement and provide better understanding of the metabolic signature of this tumor not seen with conventional MRI. Metabolic progression defined by increased levels of total choline concentration in serial MRS preceded clinical decline by 2.4 ± 2.7 months. This shows that MRS could serve as an important and early surrogate marker for disease progression, often not seen on MRI [85]. Single-voxel spectroscopy and MRS showed a strong correlation in metabolic profile of these tumors and could provide proper assessment of tumor response with treatment in these tumors [86]. Evaluation of the tumor perfusion/cerebral blood flow and tumor volume correlated with response to radiation in patients with DIPG. This study demonstrated that neither tumor volume nor cerebral blood flow at baseline, during and postradiation was associated with improved OS, but larger tumors at presentation and increased tumor perfusion showed slight favorable OS ($p = 0.41$) [87]. Newer discernment shows that subtle ‘occult’ enhancement of these tumors not seen readily on conventional MRI could be ascertained by subtracting precontrast from postcontrast T1 images. These areas of occult enhancement corresponded to areas of higher cerebral blood volume and could be a surrogate marker of increased angiogenesis induced by hypoxia not seen on conventional MRI [88]. A recent study

suggests diffusion metrics like ADC can define clinically distinct subgroups of pediatric DIPG. Those tumors with lower ADC at initial presentation was predictive of a more clinically aggressive variant and correlated with a higher grade tumor (III/IV), whereas higher ADC was noted in tumors with grade II histology. In tumors with high ADC, *K27M* mutation was seen which is known to be present in 70% of DIPG. Although this study is limited by its small sample size, it provides an interesting observation and the role of ADC as a useful noninvasive prognostic marker [89]. Re-irradiating these tumors is often performed when they progress. Understanding the corticospinal tract anatomy before and after progression and re-irradiation of these tumors has not been well defined. Feasibility of evaluating serial changes in FA values using DTI seemed to provide more correlative information with tumor response. The likely efficacy of complementing DTI analysis to conventional neuroimaging to better understand response to re-irradiation of progressive DIPG may be beneficial [90].

Conclusion

DIPG has continued to be biologically elusive and therapeutically frustrating, undermining all research endeavors over the last two decades. However, over the last few years, profile of the diversity, quality and quantity of the scientific efforts pursued against these tumors provide reason for therapeutic optimism. Unprecedented

work to better understand the biology and genomic signature continues. Inter-tumoral heterogeneity with biologic subgroups is now being identified, providing better clues and rationality while designing future trials. With recent surge in the success of developing experimental models, better preclinical studies and therapeutic testing can now be performed. This would help in improved comprehending of drug selection and understanding the mechanistic of resistance. Endeavors should continue to develop and improve locoregional delivery techniques of biologic agents obviating systemic toxicity, and improvisation of noninvasive imaging techniques to follow tumor response pattern. These newer discoveries and endeavors provide hope and therapeutic optimism.

Future perspective

Therapeutic success in treating this formidable and lethal tumor could happen if sustained pursuance in exploration of innovative methods and identification of efficacious treatment paradigms continues. With DIPG now known to have intertumoral heterogeneity therapeutic challenges have surfaced. Small biopsies performed may not be truly representative of the tumors and designing trials based on that may be

inadequate. Thus the need to improvise neuro-surgical techniques in the future to perform more robust surgeries and obtain liberal biopsies from various parts of this tumor, is now needed to individualize optimal therapy. Developing pre-clinical models to better understand signaling pathways and mechanism of drug resistance need to be further explored. Improvisation of immunotherapeutic strategies and locoregional delivery of newer biologic agents would be the field for the next decade. Finally global collaborative efforts should continue, as it is only then we can hope to obtain an ideal multifaceted therapeutic approach against DIPG. We remain optimistic and hope this decade would provide success in stalling the relentless progression of this tumor and find a cure.

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