REVIEW

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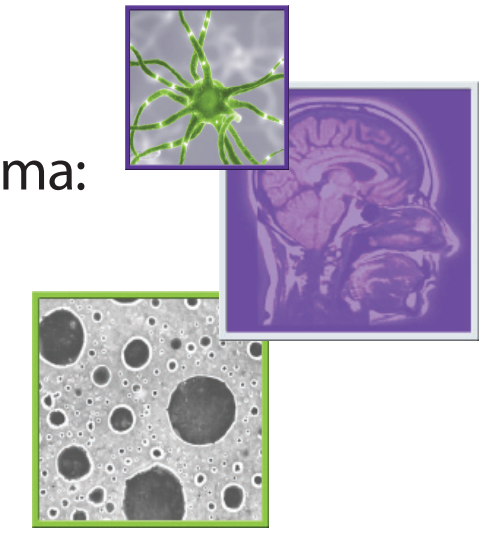
Pediatric diffuse intrinsic pontine glioma: can optimism replace pessimism?



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Practice Points

- Introduction
  - Diffuse intrinsic pontine glioma (DIPG) represents 10–15% of all pediatric brain tumors and occurs at a peak age of 6–8 years.
  - Diagnosis is based on a classical history (<3–6 months) consisting of cranial nerve deficits, long tract signs and ataxia and, when accompanied by typical MRI, histological confirmation by biopsy is usually not performed.
  - Despite numerous clinical trials, the only proven therapy is conventional radiotherapy, which for the vast majority remains a palliative measure only.
  - Prognosis is very poor with a median survival of less than a year; more children die from DIPGs than any other brain tumor.
- Reasons for failure in DIPG?
  - There is a historical lack of DIPG tumor samples and a hampered knowledge of the biology of DIPG.
- Poor understanding of the biology of DIPG
  - Recent increased access to tumor material from autopsy and the reintroduction of biopsy by some study groups has started to produce exciting insights into the specific and unique underlying molecular biology of DIPG compared with both pediatric and adult nonbrainstem malignant gliomas.
- Lack of preclinical models for DIPG
  - Preclinical cell line and animal models specific for DIPG are now emerging based on new biological insights of the disease. These will allow more rapid and accurate testing of novel therapeutics.
- Poor drug delivery
  - Concerns over limited drug distribution in DIPG have prompted a renewed interest in developing improved drug delivery techniques suitable for the brainstem and children.

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SUMMARY Pediatric diffuse intrinsic pontine glioma (DIPG) has a dismal prognosis that has not seen a change in outcome despite multiple clinical trials. Possible reasons for failure to make progress in this aggressive childhood brain tumor include: poor understanding of the underlying molecular biology due to lack of access to tumor material; absence of accurate and relevant DIPG preclinical models for drug development; ill-defined therapeutic targets for novel agents; and inadequate drug delivery to the brainstem. This review will demonstrate that systematic studies to identify solutions for each of these barriers is starting to deliver progress that can turn pessimism to optimism in DIPG.

Pediatric diffuse intrinsic pontine glioma (DIPG) remains one of the greatest challenges in the field of pediatric oncology and has been surrounded by pessimism for many decades. DIPG represents 10–15% of childhood brain tumors and has a peak incidence of 6–8 years [1]. It is characterized by a typical history of a triad of neurological deficits (ataxia, cranial nerves and long tract signs), which, at presentation, are usually less than 3 months in duration. Other presenting symptoms and signs occur less frequently as a result of raised intracranial pressure, behavioral manifestations and disseminated lesions [1–5]. The diagnosis is conventionally based on the combination of this classical history and typical MRI features without recourse to histological confirmation by biopsy [6]. When a tumor sample is available, the histology is usually consistent with a malignant astrocytoma [7]. Conventional radiotherapy remains the only proven effective therapy, that, unfortunately for the majority of patients, is palliative in nature. The prognosis for DIPG is dismal, with a median survival of 8–11 months, with very few patients surviving past 2 years [1,8].

Over four decades of multiple clinical trials have tried and failed to improve the outcome for patients with DIPG and these have been extensively and critically appraised in two previous reviews that provide an excellent summary of DIPG clinical studies from 1984 to 2011 [1,8]. However, this article will focus on the possible barriers as to why we have failed to make progress in DIPG and suggests that recent developments give cause for optimism that improvements in survival can be achieved in this devastating disease.

Reasons for failure in DIPG?

DIPG is not the only brain tumor of childhood with a poor prognosis but, owing to its unique anatomical location within the brainstem, there are specific reasons that have hampered progress and these will be discussed, highlighting recent advances and possible solutions.

■ Lack of DIPG tumor samples

Tumor tissue can be obtained by surgical biopsy at the time of diagnosis or from a post-mortem autopsy. The resulting tumor tissue can be used to confirm the histological diagnosis but also provides vital material for biological research. Unfortunately, the rarity of both diagnostic biopsy and autopsy has meant a lack of DIPG tumor samples and this has resulted in a critical lack of molecular studies and specifically a delay in applying the latest high-coverage, rapid-throughput genomic profiling and sequencing techniques compared with other tumors. Although now not standard practice to biopsy typical DIPG, in the past such biopsy was undertaken. When computed tomography imaging was first introduced it was difficult to separate good prognostic focal low-grade brainstem tumors (medulla, mid-brain and dorsal pons) from the more common (80%) aggressive diffusively invasive pontine tumors without pathological examination, and biopsy was recommended [9]. However, the advent of MRI allowed an accurate radiological-based classification of low-grade and diffuse brainstem tumors and resulted in a change in recommendation for MRI scans to replace biopsy in diffuse brainstem tumors [6]. Since that time, there has been a vigorous debate about the role of biopsy in DIPG for both standard clinical care and for research purposes [10–12]. This debate has centered on the safety of the procedure in relation to any individual benefit for the patient and the ethics of conducting biopsy for research purposes only. Recent and indeed past evidence has confirmed the relative safety of stereotactic biopsy in childhood DIPG, with very low or no mortality and usually transient morbidity only reported [13,14]. The argument for biopsy includes achieving a histological diagnosis; however, for patients with a classical clinical radiological presentation, the

pathology diagnosis is highly likely to be consistent with a DIPG (rare for another tumor or nontumor diagnoses) and, therefore, the main justification currently for performing a diagnostic biopsy for a typical DIPG is in the context of translational research in a clinical trial. Recent studies applying advanced molecular techniques have proven that, even with small diagnostic biopsy tumor samples, meaningful and significant insights into the underlying biology of DIPG can be achieved [15]. This has renewed the discussion about including biopsy for DIPG within clinical trials either for pure research purposes or possibly to stratify patients on the basis of putative biological targets [12,14].

To overcome the ethical and practical issues associated with diagnostic biopsy of DIPG, a number of groups have recently concentrated on applying modern molecular techniques to analyze both historic and prospectively collected post-mortem DIPG tumor samples [16–19]. The groups from St Jude's and Toronto Children's hospitals have demonstrated the practical and technical possibilities of obtaining and analyzing autopsy material from the patient/family perspective and that of the research team [7,20]. Satisfactory DNA and RNA quality was obtained in the majority of prospectively collected cases and, in some cases, it was even possible to establish primary tumor cultures from material at the time of autopsy [18,21]. Although tumor material at post-mortem represents end-stage pretreated disease, comparison between autopsy and biopsy studies demonstrates the validity and benefit of using both approaches to study the molecular biology/pathology of DIPG [15–17,19,21,22].

It is apparent from the recent number of high-quality peer-reviewed publications reporting on new molecular findings in DIPG that the systematic efforts of clinicians, scientists and parent/family groups to obtain ethically approved post-mortem and biopsy tumor samples has been a major and vital step forward for research in DIPG.

Poor understanding of the biology of DIPG

As a direct consequence of the lack of tumor material, much of the prior knowledge of the molecular biology of DIPG was based on data from either limited series or extrapolated from samples of malignant glioma in children or adults arising from nonbrainstem locations. If such extrapolation is valid it is necessary to know the answer to the following two questions: are DIPGs and nonbrainstem pediatric high-grade gliomas (pHGGs) biologically the same and do they share a common molecular pathology with their adult counterparts? Until recently, there was no clear answer to these questions, which has meant that the majority of therapeutic strategies for DIPG have been adapted from clinical trials in adult high-grade glioma (aHGG) and this may be one possible explanation for the failure to make progress in childhood pontine glioma.

Recent molecular data from both autopsy and biopsy studies are starting to clarify the biological relationship between DIPG and pHGG/aHGG. Comparison of chromosomal abnormalities has generally showed that pHGGs harbor fewer DNA copy number changes than aHGG, as illustrated by gain of chromosome 7 (12 vs 74%) and loss of 10q (27 vs 80%) [16,23–26]. A consistent finding in both pHGG (20%) and DIPG (47%) compared with aHGG (9%) is a gain of 1q, whereas the finding of a 'stable genome' pattern is mainly restricted to pHGG, being rarer in DIPG and not seen in aHGG. Abnormalities in both the Rb and P53 pathways appear more frequently in DIPG than pHGG and, in this respect, DIPG resembles aHGG. However, one key difference between DIPG and both pHGG and aHGG is the rarity of the deletion of *CDKN2A/B* in DIPG (2%) [15–17,19,21,22,25,27,28]. Gene expression profiling studies demonstrate that, although DIPG, pHGG and aHGG share some common features, DIPG cases can be distinguished from both pHGG and aHGG; interestingly, thalamic pHGG tends to cluster closely with DIPG [21,22]. Proposals have been made for a molecular classification system for aHGG, pHGG and most recently DIPG but debate continues as to whether any system can accommodate these related yet distinct subtypes of malignant glioma [17,21,29–32].

Focal amplifications and deletions are reported most commonly in aHGG, followed by DIPG, with fewer events described in pHGG. This is illustrated by amplified *EGFR* (>40% in aHGG, 40% in DIPG and 6% in pHGG), while *PDGFRA* amplification is most common in pediatric tumors (10% in aHGG, 28% in DIPG and 14% in pHGG) [17,22,25,26,33–38]. DIPG also demonstrates focal amplification events in several other receptor tyrosine kinases, including *MET*, *IGF1R* and *ERBB4*, with co-amplification occurring in the same tumor, such as dual amplification of *PDGFRA*/*MET* and *PDGFRA*/*IGF1R*. Focal amplifications affecting

the PI3K pathway, including *HRAS*, *KRAS*, *AKT* and *PIK3CA*, have been found in DIPG (38%) at a higher rate than in pHGG (24%), but less frequently than in aHGG [15–17,19,21,22,24,27,28]. The frequency and pattern of gene mutations have perhaps illustrated most distinctly the differences between DIPG, pHGG and aHGG; *P53* mutations have a similar incidence in pHGG (only 9% in <3 years) and aHGG of approximately 38%, but have been reported to be higher in DIPG (up to 71%) [39–44]. Mutations of the *IDH1* and *IDH2* genes frequently seen in secondary adult glioblastoma arising from lower-grade lesions are very infrequent in pHGG (8.6%) and then only in adolescent patients; these mutations have not been reported in DIPG [32,45–47]. The V600E activating mutation of *BRAF* seen in melanoma has been reported in pHGG (10%), but is absent in DIPG and at a higher frequency than aHGG [48–52].

A recent whole-exome gene sequencing study of pediatric glioblastoma has revealed somatic mutations of the histone H3.3–ATRX–DAXX chromatin remodeling pathway in 44% of 48 cases; this mutation appears to be restricted to children and young adults [27]. These somatic *H3F3A* mutations are also found in DIPG (60%) but it appears specific mutations occur exclusively in DIPG (*HIST1H3B*) or nonbrainstem/thalamic pHGG (*H3F3A G34R/V*) [27,28].

One explanation of why DIPG has a different biology to both pediatric and adult nonbrainstem high-grade gliomas would be that it arises from a different initiating cell that is restricted to the anatomical site and occurs at a distinct stage of development. Gene expression studies have explored differentially expressed genes between DIPG and nonbrainstem tumors that may be involved in brainstem development [17,21]. One study has identified precursor-like cells in the normal human ventral pons that occur in the same anatomical site and at the same age as DIPG, which may be induced by aberrant Hedgehog signaling [18].

It appears that DIPG and pHGG share some common genetic abnormalities, which are distinct from aHGG; however, there are significant differences between DIPG and pHGG. It would seem that simple extrapolation of data between pediatric and adult malignant glioma subtypes is no longer appropriate and that future studies should ensure that any analysis comprehensively compares and contrasts findings between the differing ages and locations of tumors.

Lack of preclinical models for DIPG

An important conclusion emerging from the observation of differences between the biology of DIPG and pediatric and adult nonbrainstem malignant glioma is the need for dedicated DIPG preclinical models. It is no longer acceptable to use either pHGG or aHGG cell lines or animal models to study the biology and novel therapeutics as a surrogate for DIPG, and recent efforts have been addressing this vital need.

Establishing immortalized cell lines for DIPG has proven to be very challenging and it is only recently that a couple of groups have reported establishment of primary DIPG cell cultures grown as neurospheres, one group using a postmortem sample and the other using biopsy tissue [18,21]. These DIPG neurospheres have been analyzed and appear to faithfully represent the corresponding primary tissue. One group used dissociated neurospheres to stereotactically transplant DIPG cells into the brains of immunodeficient mice by either a lateral ventricle or a fourth ventricle route [18]. Pathological examination of sacrificed mice demonstrated infiltrating tumor cells in the cortex, cerebellum and pons. These are currently the most genetically accurate models for DIPG, although not completely replicating the diffuse infiltrative pontine phenotype. Phenotypically appropriate models have been established using orthotopic xenotransplantation of malignant glioma cell lines directly into the brainstems of mice or rats [53–57]. Such models have used luciferase-modified human aHGG cell lines implanted into the pontine tegmentum of athymic rodents with bioluminescence imaging to allow for serial monitoring of tumor growth and, while replicating the diffuse infiltrative nature of DIPG, they do not reproduce the distinct biology. Another group has attempted to produce a more genotypically accurate model by using genetically adapted PDGF-overexpressing and INK4-deleted cells in the fourth ventricle of mice with cells that then invade the brainstem [57].

These cell line and animal models are now allowing study of biology, novel agents and drug-delivery systems focused specifically on DIPG.

Lack of novel targets & drugs

The failure of numerous clinical trials investigating conventional cytotoxic chemotherapy and single-agent targeted agents had led to an understandable pessimism in DIPG. However, with the recent rapid increase in the understanding of the

molecular biology and the emerging knowledge of the differences between DIPG, pHGG and aHGG, clearer targets for pontine glioma are starting to arise. The updated review by Hanahan and Weinberg describing their 'Hallmarks of Cancer' provides an excellent framework for considering the emerging targets and therapeutic strategies for DIPG [58]. The authors have produced a framework to help consider the complexity of malignancy, which includes the following hallmarks of cancer: genomic instability, proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis and invasion/metastases, avoiding immune destruction, deregulation of cellular metabolism and the creation of a tumor microenvironment, and interaction with neighboring nontumor cells. For DIPG, much remains to be elucidated as to which and to what extent each individual hallmark plays a role in DIPG; the classification can provide a useful framework when considering new DIPG targets and possible relevant new agents (Figure 1).

Sustaining proliferative signaling by the overexpression, amplification or constitutive mutation of receptor tyrosine kinases plays an important role in DIPG and other malignant gliomas. As already discussed, *PDGFRA, EGFR* and *IGF1R* have all been demonstrated to be upregulated in pontine glioma and have been the target of completed or ongoing clinical studies of small molecule or monoclonal antibody inhibitors as a single agent at recurrence, or in combination with radiotherapy in newly diagnosed patients. To date, the activity of single-agent inhibitors in DIPG clinical trials has been limited (Table 1), but there have been some responses reported and it may be that by selecting or enriching the study population based on target presence by using biomarkers (either from tumor material or in the future surrogate labeled imaging biomarkers) subpopulations of DIPG may be found that respond to specific targeted therapies [36,59–64]. Activation either as a result of growth factor receptor signaling or specifically from mutations/amplification of downstream

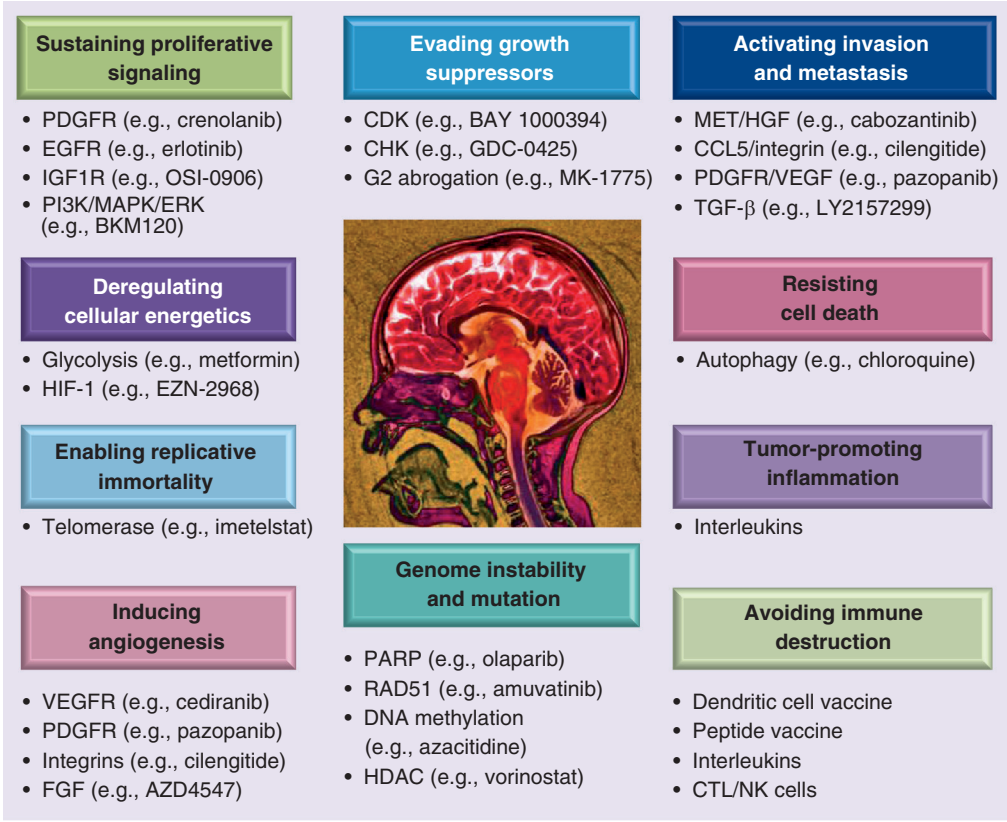

Figure 1. Possible therapeutic targets in diffuse intrinsic pontine glioma classified as per 'Hallmarks of Cancer' [58].
CTL: Cytotoxic T lymphocyte; NK: Natural killer.

Table 1. Targeted agent clinical trials in diffuse intrinsic pontine glioma.

Target	DIPG population	Objective response rate (%)	Median overall survival (months)	Median progression-free survival (months)	1-year overall survival (%)	2-year overall survival (%)	Ref.
EGFR							
Erlotinib	New with radiotherapy	17	12	8.0	50	19	[36]
Gefitinib	New with radiotherapy	14	NR	7.4	56	20	[62]
Nimotuzumab	New with radiotherapy	10	9.6	5.5	34	NR	[63]
PDGFR							
Imatinib	New with radiotherapy	3	11	NR	45	10	[59]
mTOR							
Temsirolimus	Relapse single agent	0	NR	2.5	NR	NR	[68]
Farnesyltransferase							
Tipifarnib	New with radiotherapy	NR	8.3	5.9	36	NR	[60]
Angiogenesis							
Thalidomide	New with radiotherapy	54	9	5.0	NR	0	[110]
VEGFR/EGFR							
Vandetanib	New with radiotherapy	NR	NR	NR	38	21	[64]
VEGF							
Bevacizumab	Relapse single agent	0	NR	2.5	NR	NR	[74]
Immunotherapy							
Pegylated IFN-α	New after radiotherapy	NR	NR	7.8	46	14	[111]

DIPG: Diffuse intrinsic pontine glioma; NR: Not reported.

members of core signaling pathways such as PI3K/AKT, mTOR or RAS/BRAF/MAPK has been shown to play a role in DIPG; targeting these downstream pathways alone or possibly in combination with upstream blockade may offer a more effective way of stopping the multiple proliferative signals in DIPG [48,50,65–69]. The evasion of growth suppressors is an important hallmark of all cancers, and DIPG has frequent abnormalities of the Rb and P53 pathways and, although currently difficult to target, exploiting these abnormal growth suppressor pathways with agents such as CDK or WEE1 inhibitors represent attractive possible new therapeutics for DIPG [70–72]. DIPG is characterized by its diffuse and infiltrative nature and understanding how the tumor cells promote invasion and metastasis will be vital; and recent data have suggested that the MET signaling pathway plays a role in this infiltrative phenotype with *MET* amplifications demonstrated in DIPG representing a novel target [21,73]. Although DIPG is not regarded as being as highly vascular as nonbrainstem high-grade glioma, the role of angiogenesis and the interaction of neighboring stromal cells in promoting invasion is an important area of study and has led to therapeutic intervention with inhibitors against *PDGFR*, *VEGFR* and the integrin family [59,64,74,75]. Genomic instability, and the promotion of mutations and a state of replicative immortality are underlying features of cancer and are characterized by abnormalities of housekeeping genes and DNA repair pathways and have been demonstrated in DIPG [16,25]. Several studies have suggested that overactivation of the poly(ADP-ribose) polymerase pathway may serve as a target to augment radiotherapy and cytotoxic chemotherapy [16,76,77]. More recently, two studies have identified mutations in histone encoding genes that appear relatively specific for DIPG (78%) and pHGG (22–31%) [27,28]. Histones play a critical role in the regulation of many processes, including DNA replication and repair, gene expression and maintenance of centromeres and telomeres, and hence represent a novel target. Histone deacetylase inhibitors have demonstrated some activity in malignant gliomas but research into the optimal use and development of agents against these epigenetic drivers is ongoing [78–84]. Avoidance of immune destruction and the role of the inflammatory response in cancer has been demonstrated to be important in certain cancers, and including malignant gliomas, with a variety of immunotherapy strategies being investigated including autologous dendritic cell tumor vaccines, peptide vaccines and the use of interleukins either as direct therapeutic agents or as targets [85–90]. For the first time, studies in DIPG are now starting to explore immunotherapeutic strategies with peptide vaccine studies based on DIPG-based biology data ongoing [44]. The role played by deregulation of cellular metabolism and resisting cell death remains to be confirmed in DIPG but is known to be important in other malignant gliomas and is an avenue of research that should be pursued.

The complexity of targeting the multiple processes involved in DIPG development is hugely challenging, as there is both individual patient molecular heterogeneity and also variation between cells within a single tumor, for example, *PDGFRA, IGFR* and *MET* co-amplification [15,21,22]. Such signaling redundancy means that molecular stratification to select the correct targeted therapy for individual tumors and also combination therapies with blockade of multiple pathways, including targeting of both up- and down-stream members of critically activated pathways, are likely to be required to overcome the inherent resistance that such molecular heterogeneity offers the tumor [91,92]. To add to this complexity it is highly likely that any effective treatment will need to address more than one aspect of the 'Hallmarks of Cancer' and a combination of agents directed at the different aspects of tumor cell survival will need to be considered; for example, radiotherapy plus molecularly selected targeted agent(s) against proliferative signaling and invasion, and immunotherapy to be applied concurrently or sequentially. Designing such clinical trials will require new methodology using factorial adaptive designs.

■ Poor drug delivery

Drug delivery is a major concern for all brain tumors as the CNS has evolved to protect the brain from poisonous substances (including therapeutic drugs) with a sophisticated and active blood–brain barrier (BBB). The BBB has a structural barrier that can restrict drugs based on their size, composition and electrical charge plus active drug efflux pumps (e.g., P-glycoprotein), which are able to transport drugs back across the BBB that have managed to pass the structural barrier [93]. Although many tumors may have a disrupted BBB due to abnormal 'leaky' tumor-associated vasculature, this is often only partial in nature and varies from tumor to tumor. Diffuse tumors such

as DIPG appear to have a more intact BBB and also have infiltrative tumor cells that can be quite distant from the main tumor mass and are intermixed with normal brain parenchyma. As such, DIPG poses a serious challenge in terms of drug delivery and this may be a significant reason for failure of response to many tested agents. Attempts to bypass the BBB include: active design of drugs that are small, nonpolar and lipophilic; blockade of the efflux pumps; chemical or physical disruption of the BBB; and direct delivery mechanisms [93,94]. For DIPG, the most commonly employed strategy has been chemical disruption with hyperosmotic BBB disruption (mannitol) either via intra-arterial or systemic delivery and also with the bradykinin analog RMP-7 [95–99]. Such strategies have so far not translated into increased survival in DIPG but further technological developments in the field may warrant possible further exploration [100]. Direct delivery techniques using convection-enhanced delivery (CED) have been demonstrated to be feasible in the brainstem in animal models and in limited initial human clinical trials [87,101–105]. CED involves the continuous infusion under positive pressure of a substance via an implanted catheter, and recent technical advances have improved delivery and safety. Agents that may be considered for CED include chemotherapy, targeted agents (small molecules and antibodies), conjugated immunotoxins, viral therapies and targeted radioisotopes. More exploratory novel delivery techniques include intranasal delivery, focused ultrasound BBB disruption and the use of nanoparticles to package and facilitate drug delivery [106–109].

Conclusion & future perspective

Over the next 5–10 years, the recent and future comprehensive genomic interrogation of biopsy- and autopsy-derived samples of DIPG will translate into the identification of new targets for pediatric pontine glioma. These targets will be validated by systematically screening novel therapeutics in recently developed cell and animal DIPG model systems to allow the prioritization of promising single-agent and combination strategies for clinical trials. New drug-delivery systems will be tested in these phenotypically accurate animal models to try and optimize the targeting of these validated targets prior to clinical trials. To better select and stratify patient cohorts according to molecular targets, there will be an increase in safely conducted biopsies at the time of diagnosis and postexposure to novel agent, which will allow pharmacokinetic (direct evaluation of drug exposure within the tumor) and pharmacodynamic (effect of the drug on the molecular target) evaluation in DIPG clinical trials. This will require international cooperation to allow larger studies for sufficient patient numbers to allow stratification and treatment assignment into study cohorts according to target presence. By examining and addressing the reasons why we have failed to make progress in DIPG a new era of science-based therapies may allow those involved in investigating and treating patients with pontine glioma to be able to look to the future with more optimism.

Financial & competing interests disclosure

D Hargrave has previously held (paid and unpaid) consultancy agreements and contributed to advisory boards with the following organizations: Genentech, GlaxoSmithKline, Hoffman-La Roche, Merck Sharp & Dohme and Novartis. However, the author confirms that all opinions expressed in this article are the author's own and not influenced by any external agency or organization. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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