Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

International meeting of the French Society of Neurology 2023

Oncolytic virotherapy for the treatment of pediatric brainstem gliomas

Jaime Gállego Pérez-Larraya [a,b,d,*], *Marc García-Moure* [a,d], *Marta M. Alonso* [a,c,d]

[a] *Program in Solid Tumors, Center for Applied Medical Research, Pamplona, Navarra, Spain*
[b] *Department of Neurology, Clínica Universidad de Navarra, Pamplona, Navarra, Spain*
[c] *Department of Pediatrics, Clínica Universidad de Navarra, Pamplona, Navarra, Spain*
[d] *Health Research Institute of Navarra (IdiSNA), Pamplona, Navarra, Spain*

INFO ARTICLE

Article history:
Received 24 February 2023
Received in revised form
20 March 2023
Accepted 23 March 2023
Available online 13 April 2023

Keywords:
DIPG
Brainstem glioma
Virotherapy
Delta-24-RGD
Oncolytic virus

ABSTRACT

Diffuse intrinsic pontine glioma (DIPG) is the most frequent brainstem glioma and the most lethal brain tumor in childhood. Despite transient benefit with radiotherapy, the prognosis of children with this disease remains dismal with severe neurological morbidity and median survival less than 12 months. Oncolytic immunovirotherapy is emerging as a potential therapeutic approach in neuro-oncology. The oncolytic adenovirus Delta-24-RGD has shown efficacy in adult patients with recurrent GBM. Our group has demonstrated that Delta-24-RGD has oncolytic activity and triggers immune response in preclinical models of DIPG, and has a synergistic effect with radiotherapy in animal models of this disease. In this scenario, we conducted a first-in-human phase 1 clinical trial to evaluate the safety and efficacy of intratumoral injection of Delta-24-RGD in pediatric patients with newly diagnosed DIPG prior to standard radiotherapy. The study confirmed the feasibility of this treatment with an acceptable safety profile and encouraging efficacy results. Correlative analyses showed a biological activity from Delta-24-RGD in DIPG. Further advanced trials are needed to validate these results. Meanwhile, plenty of opportunities to increase the potential contribution of oncolytic viruses in the management of devastating tumors with no current effective treatment such as DIPG need to be explored and exploited.

1. Overview of diffuse intrinsic pontine glioma

Brainstem gliomas are a heterogeneous group of tumors with varying degrees of aggressivity and prognosis depending on their clinical presentation, location, and molecular characteristics. Most of them arise within the pons, the majority of which are poor prognosis high-grade infiltrative tumors. On the contrary, pediatric tumors located in other areas of the brainstem, such as the mesencephalic tectum or the cervicomedullary junction, are more likely to be low-grade well-circumscribed tumors with better prognosis [1,2].

* *Corresponding author at*: Department of Neurology, Clínica Universidad de Navarra, Avda. Pío XII n°36, 31008 Pamplona, Spain.
E-mail address: jgallego@unav.es (J. Gállego Pérez-Larraya).

https://doi.org/10.1016/j.neurol.2023.03.016

The clinico-radiological entity widely known as diffuse intrinsic pontine glioma (DIPG) accounts for most of the tumors occurring in the brainstem and represents about 10–15% of all brain tumors in children and adolescents. It has an estimated incidence of 1–2 cases per 100,000 population, with a peak at ages between 5 and 10 years [3,4]. These figures and the fact that it rarely occurs in adult patients reflect a potential pathogenic link with the process of brain development, involving possibly the neural precursor-like cell populations located in the ventral pons [5].

Autopsy tissue and biopsy samples have recently led to important advances in the understanding of the molecular biology of these tumors. Irrespective of purely histopathological features, important genomic and molecular alterations have been identified in DIPG [6]. The hallmark of these genetic events is histone mutations, likely representing the first genomic event and the driver for oncogenesis in DIPG [7]. Mutually exclusive somatic mutations in *H3F3A* and *HIST1H3B* are found in nearly 80–90% of these tumors, which result in a lysine-to-methionine substitution at position 27 on the H3.3 and H3.1 histone tail (H3K27M), respectively [6,8,9]. Other frequent genomic alterations involved in the tumorigenesis of this tumor include *TP53* mutations, which along with amplification and overexpression of platelet-derived growth factor receptor A (*PDGFRA*), frequently co-occur in H3.3-mutant tumors. On the other hand, H3.1-mutant tumors usually carry mutations in the activin A receptor type 1 (*ACVR1*) and the PI3-kinase pathway [6,10,11]. Contrary to what happens in adults' brainstem gliomas, mutations in the isocitrate dehydrogenase type 1 (*IDH1*) or type 2 (*IDH2*) genes are extremely rare in pediatric DIPG but not impossible [12]. The updated 2021 World Health Organization *Classification of the central nervous system tumors* (CNS) defines pediatric diffuse midline gliomas according to molecular characteristics, particularly the presence or absence of histone mutations [13], which indeed is not necessarily synonymous with the clinico-radiological entity of DIPG.

Reflective of the anatomic location of the tumor in the pons and its aggressive behavior, children with DIPG usually present with rapidly evolving cranial nerve palsies, more frequently sixth and seventh neuropathies, pyramidal signs such as paresis with hyperreflexia and Babinski sign, and cerebellar signs like dysarthria, ataxia, and dysmetria.

Along with the clinical picture, magnetic resonance imaging (MRI) is the imaging tool of choice for supporting the diagnosis of DIPG. MRI findings typically consist of a diffuse infiltrative lesion expanding the pons, with T2-hyperintense and T1-hypointense signals, and generally with no contrast enhancement.

Because of its location in such an eloquent region and the fear of surgery-related neurological morbidity, the diagnosis of DIPG has traditionally relied on compatible clinical and neuroimaging features alone, with no histopathological confirmation usually needed to proceed with antitumor treatment [14]. However, advances in neuroimaging and surgical techniques have prompted a shift in this tendency, with several studies having demonstrated that biopsy of DIPG can be safely done with a very low complication rate, thus ensuring an accurate histo-molecular diagnosis with some prognostic and therapeutic implications [15,16].

Conventional radiation therapy administered in daily fractions of 1.8 Gy to a total dose of 54–59.4 Gy still remains the standard of care for children suffering from this disease [17]. Treatment is however palliative since, despite initial benefit, most patients recur within a few months [18,19]. In the absence of more effective therapies, the prognosis of children with DIPG is dismal: DIPG represents the leading cause of brain-tumor-related death in the pediatric population, with median survival times not exceeding 10–12 months and with less than 10% of patients surviving beyond 2 years from diagnosis [3,4]. In this scenario of lack of therapeutic progress over the past decades, novel therapeutic approaches are urgently needed.

2. Virotherapy as a therapeutic tool for gliomas

2.1. *Immunovirotherapy in neuro-oncology*

Oncolytic immunovirotherapy is emerging as an alternative therapeutic approach for cancer. One of the rationales behind the use of genetically engineered or attenuated naïve viruses to treat cancer is their ability to selectively replicate in tumor cells and induce their lysis. In addition to this intrinsic tumor cytolytic effect, oncolytic viruses are capable of promoting inflammation and eliciting both innate and adaptative anti-tumor immune responses [20] (Fig. 1).

In the past years, various preclinical and clinical studies have specifically addressed the development and potential of this innovative treatment modality in neuro-oncology, mostly in adult high-grade diffuse gliomas [21]. Several phase I and II clinical trials with both DNA viruses (such as adenovirus, herpes simplex virus-1, parvovirus, and vaccinia virus) and RNA viruses (like Newcastle virus, measles virus, poliovirus, and reovirus) have already been conducted or are currently ongoing in this patient population. Despite the high variety of oncolytic virus platforms, routes of administration, and delivery methods, most of these early clinical studies have suggested the feasibility and safety of this therapeutic approach, and promising traces of antitumor effect and clinical benefit have also been shown [22,23].

The favorable safety data observed in such adult patient trials and promising results in preclinical research have prompted the expansion of this potential treatment modality to the pediatric population. Concretely, a dose-escalation phase I trial of intratumoral administration of the herpes simplex virus-1 G207 alone or in combination with radiotherapy in 12 children and adolescents with recurrent supratentorial brain tumors revealed an acceptable adverse event profile and showed evidence of radiographic, neuropathological or clinical responses in most of the patients. Correlative studies demonstrated that treatment markedly increased the number of tumor-infiltrating lymphocytes [24]. Another recent dose-escalation phase I trial with the intravenous reovirus Pelareorep in combination with subcutaneous GM-CSF conducted in 6 pediatric patients with diverse recurrent supra- and infra-tentorial high-grade brain tumors also showed acceptable tolerance but lack of efficacy at the administered doses [25]. Currently, an ongoing phase Ib

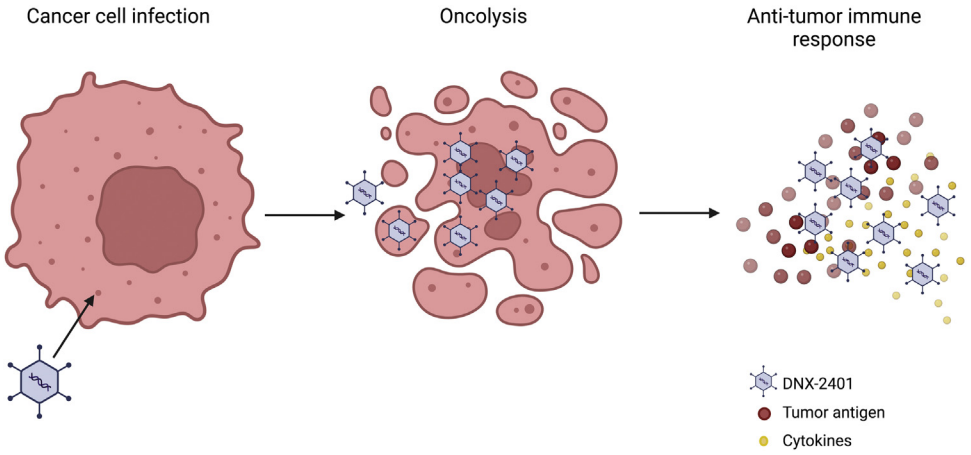

Fig. 1 – Double mechanism of action of oncolytic viruses, inducing a direct oncolytic effect and triggering an immune response. Created with BioRender.com.

trial is investigating the safety of intratumoral convection-enhanced delivery of the oncolytic poliovirus PVSRIPO in pediatric patients with recurrent WHO grade 3 or 4 malignant glioma (NCT03043391).

2.2. *Delta-24-RGD*

Our group's research is based on the Delta-24-RGD oncolytic virus platform. This is an oncolytic serotype 5 adenovirus engineered with two genetic modifications conferring selective replication and enhanced infectivity in tumor cells, respectively. The first genetic modification is a 24-base pair deletion (Delta-24) in the E1A viral gene, which abrogates the interaction between the mutated E1A protein and the normal retinoblastoma (Rb) protein. This results in the inability of the virus to replicate in normal cells with functional Rb pathway, with viral replication being selectively confined to those cells with abnormal or dysregulated Rb pathway, i.e., tumor cells [26,27]. The second modification consists of the addition of an arginine-glycine-aspartic acid (RGD) motif into the viral fiber H-loop, which enables its interaction with the surface integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ thus increasing its capacity to enter or infect the tumor cells (Fig. 2). Contrary to what happens with the natural receptor for adenovirus, i.e., the coxsackie-adenovirus (CAR) receptors, these integrins are typically overexpressed on tumor cells, including glioma cells [28,29].

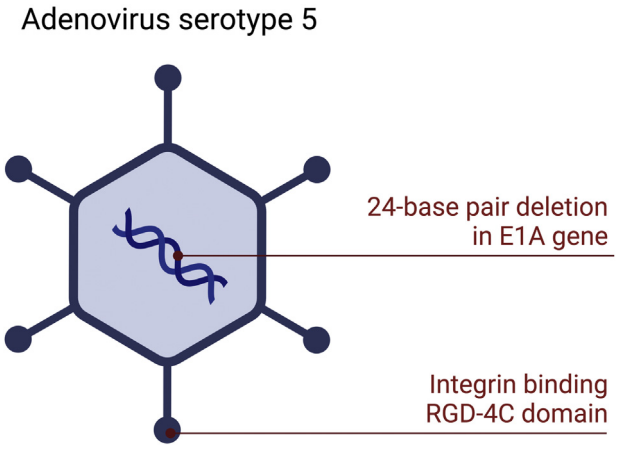

Fig. 2 – Genetic modifications of the Delta-24-RGD oncolytic adenovirus, responsible for selective replication and enhanced infectivity in cancer cells. Created with BioRender.com.

Following the demonstration of both a direct oncolytic effect and the induction of specific antitumor immune response in glioma cells [27,29,30], single intratumoral administration of different doses of Delta-24-RGD was tested in 37 adult patients with recurrent glioblastoma (GBM) in a phase I clinical trial aimed at evaluating its safety, efficacy, and mechanism of action [22]. The study revealed that treatment with up to 3×10^8 viral particles (vp) was safe with no dose-limiting toxicity observed and was associated with clinical benefit with long-term survival in a subset of patients and with a more than 95% contrast-enhancing tumor reduction in 3 patients. Analysis of post-treatment surgical samples proved viral replication and spread within the tumor with direct virus-induced oncolysis, as well as tumor infiltration by CD8+ and T-bet+ cells, evidencing the elicitation of an immune-mediated antiglioma response [22]. Another recent phase I trial showed the feasibility of convection-enhanced delivery of this oncolytic virus in patients with recurrent GBM [31].

3. Preclinical development of immunovirotherapy for DIPG

The aforementioned data on the safety and potential efficacy of Delta-24-RGD in adult patients with GBM and the need for new and more effective treatments in children suffering from the devastating DIPG, led our group to narrow the focus and explore this innovative therapy in such a pediatric cancer population.

The first step for this purpose consisted of developing a reproducible and frameless in vivo DIPG model that allows for rapid evaluation of tumorigenicity and efficacy of intratumo-

rally delivered therapeutic agents in the preclinical setting [32]. This model is based on an implantable guide-screw system [33] inserted in the skull of the mouse according to posterior fossa anatomic landmarks and directed to the pontine area, without the need for a stereotactic frame. In addition to delivering cells and thus generating tumors in the pons in a fast and reproducible manner, it allows direct intratumoral delivery of oncolytic viruses or other therapeutic drugs [32].

Afterward, the antiglioma effect of Delta-24-RGD was evaluated in DIPG models [34]. After confirming both CAR and integrins expression and viral replication, the antiglioma effect was demonstrated in vitro in a panel of cell lines and in vivo in immunosuppressed and immunocompetent orthotopic DIPG models. Delta-24-RGD resulted in a direct oncolytic effect. Importantly, viral in vivo administration also triggered an immune response with marked active T cell infiltration mainly circumscribed in the tumor mass, leading to a significant increase in the survival of treated mice. Of note, dose-escalation studies confirmed the lack of toxicity in the immunocompetent murine DIPG models [34].

Since radiation therapy is the standard of care for DIPG, and on the basis that adenoviral infection inhibits the cellular DNA repair machinery to increase its replication potency and thus could radiosensitize infected tumor cells [35,36], a further study evaluating the combination of Delta-24-RGD with radiotherapy in DIPG models was conducted [37]. Indeed, this study showed that Delta-24-RGD led to the downregulation of relevant DNA damage repair proteins. The combination of oncolytic virotherapy and radiotherapy resulted in a synergistic antiglioma effect with increased cytotoxicity and survival in treated mice compared to either treatment alone. Notably, the combined treatment significantly increased the trafficking of immune cells (CD3, CD4+, and CD8+) to the tumor niche compared with single treatments [37].

4. Translation to clinics: phase I clinical trial

These encouraging results obtained in the preclinical field motivated the translation of Delta-24-RGD to the clinic in a dose-escalation phase I clinical trial [38]. The study was conducted in 12 children and adolescents with newly diagnosed DIPG and was aimed at evaluating the safety and efficacy of the intratumoral injection of Delta-24-RGD prior to standard radiotherapy. A stereotactic biopsy was performed through the middle cerebellar peduncle, and thereafter the virus was intratumorally delivered using the same biopsy tract.

Intratumoral delivery of DNX-2401 at both doses of 1×10^{10} and 5×10^{10} had an acceptable tolerance, with no dose-limiting toxicity. Most adverse events were mild to moderate and mainly consistent with the underlying disease or with the surgical procedure and were medically manageable. Three clinically serious adverse events were observed, and only one of them (transient hemiparesis) was probably related to the procedure. The most frequently reported adverse events, in general, were asthenia, headache, and vomiting, while the most frequent events at least possibly related to DNX-2401 were vomiting and pyrexia. Concerning efficacy, reductions in tumor area were observed in 9 out of 12 patients, and 3 patients achieved a confirmed partial response according to RAPNO criteria [39] (Fig. 3). Median overall survival, regardless of DNX-2401 dose, was 17.8 months. Notably, survival rates at 12 and 18 months were 75% and 50%, respectively [38].

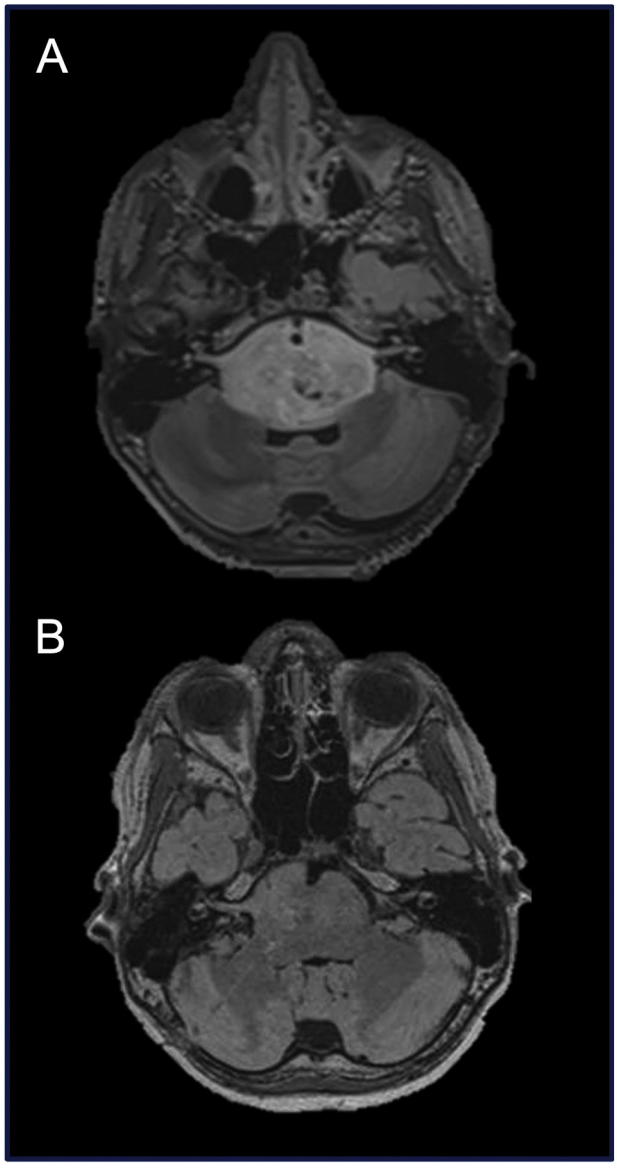

Fig. 3 – Example of tumor area reduction on magnetic resonance imaging (MRI). Axial FLAIR MRI before (A) and 3 months after (B) Delta-24-RGD administration and completion of radiotherapy.

Immunophenotyping of tumor samples obtained prior to virus infusion showed scarce CD8 and CD4 T cell infiltration, with myeloid cells being the most abundant immune population, consistent with an immunosuppressive tumor microenvironment. Analysis of tumor samples at recurrence from one patient revealed a reshaping of the tumor microenvironment with increased CD8+ and CD4+ T cell infiltrates and a marked drop in the myeloid compartment. Single-cell RNA sequencing at that timeframe showed up-regulation of pathways in tumor-infiltrating macrophages associated with

viral processes and enhanced immune response, including overexpression of proinflammatory cytokines [38].

5. Future directions

In addition to the observed safety and efficacy outcomes, this latter study has shown evidence of biological activity from Delta-24-RGD in DIPG. Altogether, these data provide the rationale for expanded testing in a multi-center phase 2 trial designed to further evaluate and confirm the safety and efficacy of Delta-24-RGD and radiation therapy in children with DIPG.

In addition, the future landscape of oncolytic immunovirotherapy for DIPG and other gliomas appears encouraging, and plenty of opportunities to increase the potential of this therapeutic approach. There is a wide range of possibilities for developing new-armed viruses with molecules that modulate the immune response in order to overcome the immunosuppressive brain-tumor microenvironment and thus enhance its antiglioma effect [21,40].

It is in this spirit, for example, new oncolytic adenoviruses have been engineered, such as Delta-24-RGDOX and Delta-24-ACT, which contain the same modifications of Delta-24-RGD but additionally incorporate OX40 and 4-1BB ligands, respectively. Both OX40 and 4-1BB are co-stimulatory receptors of the TNF superfamily, and the objective of developing these new viruses is to induce the expression of such molecules in the tumor cells and so increase the antitumor immune response, as has recently been proven in DIPG models [41–43].

Moreover, apart from new-armed viruses with enhanced immune effect, the ability of oncolytic viruses to reshape the brain-tumor microenvironment can be of great interest for combination strategies with other immune-oncology agents such as immune-checkpoint inhibitors and chimeric antigen receptor T cell therapy [20].

The potential contribution of oncolytic virus platforms in the management of devastating tumors with no current effective treatment, such as DIPG, merits further investigation and development since they might already be here to stay.

Disclosure of interest

The authors declare that they have no competing interest.

REFERENCES

[1] Guillamo JS, Doz F, Delattre JY. Brain stem gliomas. Curr Opin Neurol 2001;14(6):711–5.

[2] Monje M, Mitra SS, Freret ME, Raveh TB, Kim J, Masek M, et al. Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. Proc Natl Acad Sci U S A 2011;108(11):4453–8.

[3] Ostrom QT, de Blank PM, Kruchko C, Petersen CM, Liao P, Finlay JL, et al. Alex's Lemonade stand foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol 2014;16:x1–35.

[4] Cooney T, Lane A, Bartels U, Bouffet E, Goldman S, Leary SES, et al. Contemporary survival endpoints: an international diffuse intrinsic pontine glioma registry study. Neuro Oncol 2017;19(9):1279–80.

[5] Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved in the formation of trace memories. Nature 2001;410(6826):372–6.

[6] Kline C, Jain P, Kilburn L, Bonner ER, Gupta N, Crawford JR, et al. Upfront biology-guided therapy in diffuse intrinsic pontine glioma: therapeutic, molecular, and biomarker outcomes from PNOC003. Clin Cancer Res 2022;28(18):3965–78.

[7] Castel D, Philippe C, Calmon R, le Dret L, Truffaux N, Boddaert N, et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol 2015;130(6):815–27.

[8] Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 2012;44(3):251–3.

[9] Nikbakht H, Panditharatna E, Mikael LG, Li R, Gayden T, Osmond M, et al. Spatial and temporal homogeneity of driver mutations in diffuse intrinsic pontine glioma. Nat Commun 2016;7:11185.

[10] Buczkowicz P, Hoeman C, Rakopoulos P, Pajovic S, Letourneau L, Dzamba M, et al. Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. Nat Genet 2014;46(5):451–6.

[11] Wu G, Diaz AK, Paugh BS, Rankin SL, Ju B, Li Y, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet [Internet] 2014;46(5):444–50 [cited 2023 Feb 24. Available from: https://pubmed.ncbi.nlm.nih.gov/24705251/].

[12] Chang EK, Smith-Cohn MA, Tamrazi B, Ji J, Krieger M, Holdhoff M, et al. IDH-mutant brainstem gliomas in adolescent and young adult patients: report of three cases and review of the literature. Brain Pathol 2021;31(4):e12959.

[13] WHO Classification of Tumours Editorial Board. Central nervous system tumours. WHO classification of tumours. 5th ed., 2021 [*6].

[14] Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. Neurosurgery 1993;33(6):1026–30.

[15] Walker DA, Liu JF, Kieran M, Jabado N, Picton S, Packer R, et al. A multi-disciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neuro Oncol 2013;15(4):462–8.

[16] Mueller S, Jain P, Liang WS, Kilburn L, Kline C, Gupta N, et al. A pilot precision medicine trial for children with diffuse intrinsic pontine glioma—PNOC003: a report from the Pacific Pediatric Neuro-Oncology Consortium. Int J Cancer 2019;145(7):1889–901.

[17] Gallitto M, Lazarev S, Wasserman I, Stafford JM, Wolden SL, Terezakis SA, et al. Role of radiation therapy in the management of diffuse intrinsic pontine glioma: a systematic review. Adv Radiat Oncol [Internet] 2019;4(3):520–31 [cited 2023 Feb 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31360809].

[18] Hoffman LM, van Zanten SEMV, Colditz N, Baugh J, Chaney B, Hoffmann M, et al. Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of Diffuse Intrinsic Pontine Glioma (DIPG): a collaborative report from

the International and European Society for Pediatric Oncology DIPG registries. J Clin Oncol 2018;36(19):1963–72.
[19] Veldhuijzen van Zanten SEM, Lane A, Heymans MW, Baugh J, Chaney B, Hoffman LM, et al. External validation of the diffuse intrinsic pontine glioma survival prediction model: a collaborative report from the International DIPG Registry and the SIOPE DIPG Registry. J Neurooncol 2017;134(1):231–40.
[20] Galanis E. Virotherapy for brain tumors — Defining the path to success. N Engl J Med 2022;386(26):2520–2.
[21] Shin DH, Nguyen T, Ozpolat B, Lang F, Alonso M, Gomez-Manzano C, et al. Current strategies to circumvent the antiviral immunity to optimize cancer virotherapy. J Immunother Cancer 2021;9(4):e002086.
[22] Lang FF, Conrad C, Gomez-Manzano C, Alfred Yung WK, Sawaya R, Weinberg JS, et al. Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma. J Clin Oncol 2018;36(14):1419–27.
[23] Desjardins A, Gromeier M, Herndon JE, Beaubier N, Bolognesi DP, Friedman AH, et al. Recurrent glioblastoma treated with recombinant poliovirus. N Engl J Med 2018;379(2):150–61.
[24] Friedman GK, Johnston JM, Bag AK, Bernstock JD, Li R, Aban I, et al. Oncolytic HSV-1 G207 immunovirotherapy for pediatric high-grade gliomas. N Engl J Med 2021;384(17):1613–22.
[25] Schuelke MR, Gundelach JH, Coffey M, West E, Scott K, Johnson DR, et al. Phase I trial of sargramostim/pelareorep therapy in pediatric patients with recurrent or refractory high-grade brain tumors. Neurooncol Adv [Internet] 2022;4(1) [cited 2023 Feb 24. Available from: https://pubmed.ncbi.nlm.nih.gov/35821679/].
[26] Fueyo J, Gomez-Manzano C, Alemany R, Lee PSY, McDonnell TJ, Mitlianga P, et al. A mutant oncolytic adenovirus targeting the Rb pathway produces anti-glioma effect in vivo. Oncogene 2000;19(1):2–12.
[27] Fueyo J, Alemany R, Gomez-Manzano C, Fuller GN, Khan A, Conrad CA, et al. Preclinical characterization of the antiglioma activity of a tropism-enhanced adenovirus targeted to the retinoblastoma pathway. J Natl Cancer Inst 2003;95(9):652–60.
[28] Bello L, Francolini M, Marthyn P, Zhang J, Carroll RS, Nikas DC, et al. αvβ3 and αvβ5 integrin expression in glioma periphery. Neurosurgery 2001;49(2):380–90.
[29] Suzuki K, Fueyo J, Krasnykh V, Reynolds PN, Curiel DT, Alemany R. A conditionally replicative adenovirus with enhanced infectivity shows improved oncolytic potency. Clin Cancer Res 2001;7(1):120–6.
[30] Jiang H, Clise-Dwyer K, Ruisaard KE, Fan X, Tian W, Gumin J, et al. Delta-24-RGD oncolytic adenovirus elicits anti-glioma immunity in an immunocompetent mouse model. PLoS One 2014;9(5):e97407.
[31] van Putten EHP, Kleijn A, van Beusechem VW, Noske D, Lamers CHJ, de Goede AL, et al. Convection enhanced delivery of the oncolytic adenovirus Delta24-RGD in patients with recurrent GBM: a phase I clinical trial including correlative studies. Clin Cancer Res 2022;28(8):1572–85.
[32] Marigil M, Martinez-Velez N, Domínguez PD, Idoate MA, Xipell E, Patiño-García A, et al. Development of a DIPG orthotopic model in mice using an implantable guide-screw system. PLoS One 2017;12(1):e0170501.
[33] Lal S, Lacroix M, Tofilon P, Fuller GN, Sawaya R, Lang FF. An implantable guide-screw system for brain tumor studies in small animals. J Neurosurg 2000;92(2):326–33.
[34] Martínez-Vélez N, Garcia-Moure M, Marigil M, González-Huarriz M, Puigdelloses M, Gallego Pérez-Larraya J, et al. The oncolytic virus Delta-24-RGD elicits an antitumor effect in pediatric glioma and DIPG mouse models. Nat Commun 2019;10(1):2235.
[35] Schwartz RA, Palacios JA, Cassell GD, Adam S, Giacca M, Weitzman MD. The Mre11/Rad50/Nbs1 complex limits adeno-associated virus transduction and replication. J Virol [Internet] 2007;81(23):12936–45 [cited 2023 Feb 24. Available from: https://pubmed.ncbi.nlm.nih.gov/17898048/].
[36] O'Cathail SM, Pokrovska TD, Maughan TS, Fisher KD, Seymour LW, Hawkins MA. Combining oncolytic adenovirus with radiation – a paradigm for the future of radiosensitization. Front Oncol [Internet] 2017;7:153 [cited 2023 Feb 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28791251].
[37] Martinez-Velez N, Marigil M, García-Moure M, Gonzalez-Huarriz M, Aristu JJ, Ramos-García LI, et al. Delta-24-RGD combined with radiotherapy exerts a potent antitumor effect in diffuse intrinsic pontine glioma and pediatric high grade glioma models. Acta Neuropathol Commun 2019;7(1):64.
[38] Gállego Pérez-Larraya J, Garcia-Moure M, Labiano S, Patiño-García A, Dobbs J, Gonzalez-Huarriz M, et al. Oncolytic DNX-2401 virus for pediatric diffuse intrinsic pontine glioma. N Engl J Med 2022;386(26):2471–81.
[39] Cooney TM, Cohen KJ, Guimaraes CV, Dhall G, Leach J, Massimino M, et al. Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 2020;21(6):e330–6.
[40] Nguyen TT, Shin DH, Sohoni S, Singh SK, Rivera-Molina Y, Jiang H, et al. Reshaping the tumor microenvironment with oncolytic viruses, positive regulation of the immune synapse, and blockade of the immunosuppressive oncometabolic circuitry. J Immunother Cancer 2022;10(7):e004935.
[41] Laspidea V, Puigdelloses M, Labiano S, Marrodán L, Garcia-Moure M, Zalacain M, et al. Exploiting 4-1BB immune checkpoint to enhance the efficacy of oncolytic virotherapy for diffuse intrinsic pontine gliomas. JCI Insight 2022;7(7):e154812.
[42] Puigdelloses M, Garcia-Moure M, Labiano S, Laspidea V, Gonzalez-Huarriz M, Zalacain M, et al. CD137 and PD-L1 targeting with immunovirotherapy induces a potent and durable antitumor immune response in glioblastoma models. J Immunother Cancer 2021;9(7):e002644.
[43] Jiang H, Rivera-Molina Y, Gomez-Manzano C, Clise-Dwyer K, Bover L, Vence LM, et al. Oncolytic adenovirus and tumor-targeting immune modulatory therapy improve autologous cancer vaccination. Cancer Res 2017;77(14):3894–907.