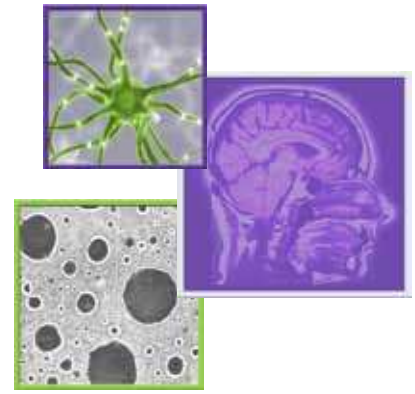
Article:
Cockle, JV, Picton, SV and Melcher, A (2013) Future clinical potential of oncolytic virotherapy for pediatric CNS tumors. CNS Oncology, 2 (4). pp. 307-310. ISSN 2045-0907

https://doi.org/10.2217/cns.13.25



Future clinical potential of oncolytic virotherapy for pediatric CNS tumors



Julia V Cockle[1] Susan V Picton[2] Alan Melcher*[1]

CNS tumors are the most common solid tumors of childhood [1]. Although treatment advances have improved survival for some pediatric CNS diseases, there unfortunately remains a group of tumors associated with significantly poorer prognosis. Among these are high-grade gliomas (HGG), which, despite aggressive management, usually recur and are associated with 5-year survival outcomes between 15–35% [2]. Diffuse intrinsic pontine glioma (DIPG), a highly malignant brainstem tumor with median survival of less than 1 year [3], remains a constant therapeutic challenge. High-risk metastatic medulloblastoma with cerebrospinal fluid dissemination at presentation is associated with 5-year survival rates between 40–70% despite intensive treatment regimens [4]. In addition, rare malignancies, such as atypical teratoid rhabdoid tumors, although often demonstrating response to chemotherapy, are associated with early relapse and a median survival of only 17 months [5]. Oncolytic virotherapy, which uses viruses to selectively infect and destroy cancer cells [6], offers a novel treatment approach for poor prognosis pediatric CNS tumors. While there is extensive literature on oncolytic virotherapy for adult brain malignancies, such as HGG, work on pediatric CNS tumors is currently only just gathering steam. With no open clinical trials focused on oncolytic virotherapy in pediatric CNS tumors we can currently only draw upon available preclinical models, alongside adult and limited pediatric clinical data, to progress the exciting future potential of this treatment modality.

The majority of preclinical studies of oncolytic virotherapy for pediatric CNS tumors evaluate efficacy in medulloblastoma. Over 15 years ago Lasner *et al.* published that herpes simplex virus (HSV) variant 1716 could infect and destroy D283 medulloblastoma cells and demonstrated that intratumoral injection of the virus into D283 tumor-bearing mice conferred a statistically significant increase in survival compared with control murine models [7]. Pyles *et al.* 1 year later also demonstrated therapeutic potential in a double mutated modified HSV strain 3616UB that was able to

> "While there is extensive literature on oncolytic virotherapy for adult brain malignancies... work on pediatric CNS tumors is currently only just gathering steam."

[1]Leeds Institute of Cancer Studies & Pathology, St James's Hospital, Leeds University, LS9 7TF, UK
[2]Yorkshire Regional Centre for Paediatric Oncology & Haematology, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX, UK
*Author for correspondence: Tel.: +44 0113 2067275; a.a.melcher@leeds.ac.uk

Future Medicine part of fsg

"Preclinical studies have demonstrated the potential for oncolytic virotherapy as a treatment paradigm for ... childhood tumors..."

replicate in, spread through and arrest growth of DAOY cell xenografts in CD17 severe combined immunodeficiency mice [8]. In 2003, Yang *et al.* established the potential of human reovirus type 3 for oncolytic virotherapy in medulloblastoma. The authors demonstrated susceptibility of medulloblastoma cells to reovirus in five out of seven medulloblastoma cell lines, as well as in primary cultures derived from surgical specimens and in two cell lines obtained from spontaneously arising tumors in Patched-1$^{+/-}$ mice [9]. Furthermore, a significant survival advantage was shown following single and multiple intratumoral injection of reovirus into DAOY cell orthotopic mouse models over controls, with multiple administrations also reducing spinal and leptomeningeal metastases [9]. More recently, Studebaker *et al.* have also demonstrated the potential for oncolytic virotherapy in treatment of disseminated disease. The authors showed that medulloblastoma cells were susceptible to killing with recombinant measles virus [10]. They then went on to generate and characterize a mouse model of disseminated disease that, when treated with intraventricular measles virus, significantly increased survival of animals when compared with controls treated with inactivated virus [11]. Other publications have demonstrated that medulloblastoma is sensitive to myxoma [12] and seneca valley virus (SVV) infection [13]. Interestingly, Yu *et al.* showed that a single tail vein injection of SVV-001 in immunodeficient orthotopic xenograft mouse models of medulloblastoma resulted in widespread infection of the xenografts, demonstrating that virus penetration through the blood–brain barrier is possible [13]. This is extremely promising in the context of the clinical applicability of oncolytic virotherapy and the potential for intravenous systemic delivery.

Unlike its adult counterpart, only a small amount of research has focused on oncolytic virotherapy for pediatric HGG, although published work has evaluated a role for HSV and SVV. Freidman *et al.* have shown that a pediatric cerebellar glioblastoma xenograft DM456 contains tumor and cancer stem cells that are more sensitive to killing by a range of modified HSVs than adult glioma xenografts [14]. One such HSV IL-12 producing virus (M002), which demonstrated killing in DM456, is thought to be particularly promising as a potential clinical therapeutic agent [15]. This is a result of its demonstrated safety in primate toxicity studies and its superior anti-tumor activity in murine models over HSV G207 [16], which has previously been used in adult glioblastoma clinical trials [17]. An adult clinical trial is in development and, if safe, it is hoped that this may progress to a pediatric trial [15]. SVV (NTX-010) was tested on a range of pediatric tumors including the brain tumors glioblastoma, medulloblastoma and ependymoma [18]. Although the most consistent cytotoxic effects were seen in neuroblastoma and rhabdomyosarcoma lines, some objective response was also seen in the glioma lines: NTX-010 was not effective on the medulloblastoma and ependymoma lines in this study [18]. Further preclinical studies evaluating the efficacy and safety of existing and emerging oncolytic viruses in pediatric HGG are required. In addition, the role of oncolytic viruses for malignancies such as atypical teratoid rhabdoid tumors and DIPG remains to be explored.

Although clinical testing of oncolytic virotherapy for pediatric CNS tumors is in its infancy, there are already a handful of encouraging reports in the literature that lay the foundations for future clinical work. Csatary *et al.* report three pediatric patients (18 months to 12 years at diagnosis) with malignant grade III/IV glioma who, following the failure of conventional treatment, went on to receive regular intravenous therapy with the Newcastle disease virus MTH-68/H for several years. At time of publication, all three patients still continued with maintenance virus therapy and demonstrated between 7–9 years survival with good quality of life [19]. Furthermore, a case report describes a 12-year-old boy with chemotherapy- and radiotherapy-resistant grade III anaplastic astrocytoma, who received intravenous and inhaled MTH-68/H alongside valproic acid. This led to dramatic regression of his original tumor; however, it did not repress the growth of two further tumors, which ultimately led to his death [20]. Encouragingly, Newcastle disease virus antigen and constituents were found in tumor tissue confirming successful systemic delivery of the virus to the tumor and demonstrating the virus's ability to infect and replicate in pediatric human cancer cells [20]. Finally, one pediatric patient, aged 11 years, was recruited into a Phase I/II trial of intravenous NVD-HUJ for recurrent glioblastoma, which overall demonstrated good tolerability, no major side effects and a complete tumor response in one other adult patient [21].

Promising results have been demonstrated in adults in terms of safety, tolerability and multiple-dose delivery data in Phase I and II clinical trials using a range of different viruses for treatment of malignant gliomas [6,17]. Recently, a handful of oncolytic virus trials for pediatric patients with non-CNS solid tumors has been developed [22], which will begin to answer questions regarding dosing, safety and efficacy of virotherapy in children. The next step for the pediatric field is to amalgamate the knowledge gained from preclinical studies together with adult and pediatric clinical observations, in order to decide which viruses to take forward to clinical trials for pediatric CNS tumors.

There are many questions that must be answered before oncolytic virus therapy reaches its full potential for pediatric patients with CNS disease. First and foremost, safety issues must be addressed. One issue that relates solely to pediatric oncology and where minimal information is known, is the effect of oncolytic viruses on the developing brain and subsequent neurodevelopmental outcomes. Although a murine study showed that intracerebral injection of modified herpes virus G207 did not adversely affect cognitive or behavioral development in young mice when compared with saline-treated controls, some mice in the treatment group developed ventriculomegaly [23]. Although the study had limitations and the authors admitted concerns that the delivery method of the virus itself may have resulted in such findings, it does raise the possibility that hydrocephalus may be a potential problem for young children receiving intracranial virotherapy and that any subsequent trials should involve monitoring for this adverse effect [23]. Furthermore, tumor location must be considered when assessing safety. In particular, brainstem tumors, such as DIPG, may be of particular concern, as local pressure generated from immune and inflammatory responses alongside viral replication may cause critical, if not fatal consequences [24]. One obvious concern for pediatricians would be the risk of uncontrollable viral replication, resulting in encephalitis and subsequent neurodevelopmental sequelae. This risk could be overcome by ensuring availability of effective antiviral treatments if significant toxicity does occur. Effective administration and delivery of the virus must also be considered. Intratumoral injection limits the number of opportunities for treatment in children, whereas systemic delivery may be fraught with problems in effectively penetrating the blood–brain barrier and overcoming the potential for neutralization of the virus by the patient's immune system before it can access its tumor target. Further research and clinical experience is required in order to optimize virus delivery to pediatric, as well as adult, intracranial tumors.

Additional questions relate to the immunotherapeutic properties of oncolytic viruses. There is clearly a fine balance between minimizing destruction of administered virus by the host immune system, while enhancing the immune system's response to kill and ablate virus-infected cancer cells [6,25]. One avenue of research is currently focused on developing cellular carriers that deliver viruses to tumors while hiding them from the neutralizing effects of the immune system [6]. Furthermore, viruses can be modified to express tumor antigens, so that when they are appropriately delivered to the immune system the anti-tumor immune response is enhanced [6]. Specific to pediatrics is the fact that young children may not yet have been exposed to naturally occurring viruses that may subsequently be used for virotherapy, and, therefore, will not have built up specific antiviral immunity [24]. Whether or not this will enhance the efficacy and/or toxicity of systemic oncolytic virotherapy in the younger age group remains to be determined. Finally, the financial and logistical difficulties in orchestrating clinical trials with adequate power in relatively rare childhood conditions must be considered, as well as the time lag to interpretation of trial results while newer and more promising viruses are developed in this rapidly evolving field.

Despite recent advances in the field of pediatric neurooncology, morbidity and mortality for this patient group remains high and novel treatment avenues for unfavorable outcome pediatric CNS tumors are desperately required [4]. Preclinical studies have demonstrated the potential for oncolytic virotherapy as a treatment paradigm for these childhood tumors, although very limited, clinical observations in children have shown promise. The next step for the field is the development and delivery of Phase I trials for pediatric CNS tumors evaluating a range of potential oncolytic viruses. This will allow the opportunity to begin to answer a range of important clinical questions. Future research will concentrate on optimizing virus delivery, modulating the role of the child's immune system to prevent viral elimination,

"...the advent of oncolytic virotherapy for pediatric CNS tumors opens the door to an exciting new era for pediatric oncology..."

enhancing anti-tumor immune responses and to evaluate the potential for synergistic interactions between oncolytic viruses and existing treatment modalities in children. Overall, the advent of oncolytic virotherapy for pediatric CNS tumors opens the door to an exciting new era for pediatric oncology with its potential to improve outcomes for the devastating disease that is cancer.

Financial & competing interests disclosure

JV Cockle is supported by a Yorkshire Cancer Research Clinical Research Training Fellowship. The authors have 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.

References

1 Heath JA, Zacharoulis S, Kieran MW. Pediatric neuro-oncology: current status and future directions. *Asia Pac. J. Clin. Oncol.* 8(3), 223–231 (2012).

2 Fangusaro J. Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology. *Front. Oncol.* 2, 105 (2012).

3 Grimm SA, Chamberlain MC. Brainstem glioma: a review. *Curr. Neurol. Neurosci. Rep.* 13(5), 346 (2013).

4 Bouffet E, Tabori U, Huang A, Bartels U. Possibilities of new therapeutic strategies in brain tumors. *Cancer Treat Rev.* 36(4), 335–341 (2010).

5 Ginn KF, Gajjar A. Atypical teratoid rhabdoid tumor: current therapy and future directions. *Front. Oncol.* 2, 114 (2012).

6 Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. *Nat. Biotechnol.* 30(7), 658–670 (2012).

7 Lasner TM, Kesari S, Brown SM, Lee VM, Fraser NW, Trojanowski JQ. Therapy of a murine model of pediatric brain tumors using a herpes simplex virus type-1 ICP34.5 mutant and demonstration of viral replication within the CNS. *J. Neuropathol. Exp. Neurol.* 55(12), 1259–1269 (1996).

8 Pyles RB, Warnick RE, Chalk CL, Szanti BE, Parysek LM. A novel multiply-mutated HSV-1 strain for the treatment of human brain tumors. *Hum. Gene Ther.* 8(5), 533–544 (1997).

9 Yang WQ, Senger D, Muzik H *et al.* Reovirus prolongs survival and reduces the frequency of spinal and leptomeningeal metastases from medulloblastoma. *Cancer Res.* 63(12), 3162–3172 (2003).

10 Studebaker AW, Kreofsky CR, Pierson CR, Russell SJ, Galanis E, Raffel C. Treatment of medulloblastoma with a modified measles virus. *Neuro. Oncol.* 12(10), 1034–1042 (2010).

11 Studebaker AW, Hutzen B, Pierson CR, Russell SJ, Galanis E, Raffel C. Oncolytic measles virus prolongs survival in a murine model of cerebral spinal fluid-disseminated medulloblastoma. *Neuro. Oncol.* 14(4), 459–470 (2012).

12 Lun XQ, Zhou H, Alain T *et al.* Targeting human medulloblastoma: oncolytic virotherapy with myxoma virus is enhanced by rapamycin. *Cancer Res.* 67(18), 8818–8827 (2007).

13 Yu L, Baxter PA, Zhao X *et al.* A single intravenous injection of oncolytic picornavirus SVV-001 eliminates medulloblastomas in primary tumor-based orthotopic xenograft mouse models. *Neuro-oncology* 13(1), 14–27 (2011).

14 Friedman GK, Langford CP, Coleman JM *et al.* Engineered herpes simplex viruses efficiently infect and kill CD133$^+$ human glioma xenograft cells that express CD111. *J. Neurooncol.* 95(2), 199–209 (2009).

15 Friedman GK, Raborn J, Kelly VM, Cassady KA, Markert JM, Gillespie GY. Pediatric glioma stem cells: biologic strategies for oncolytic HSV virotherapy. *Front. Oncol.* 3, 28 (2013).

16 Markert JM, Cody JJ, Parker JN *et al.* Preclinical evaluation of a genetically engineered herpes simplex virus expressing interleukin-12. *J. Virol.* 86(9), 5304–5313 (2012).

17 Parker JN, Bauer DF, Cody JJ, Markert JM. Oncolytic viral therapy of malignant glioma. *Neurotherapeutics* 6(3), 558–569 (2009).

18 Morton CL, Houghton PJ, Kolb EA *et al.* Initial testing of the replication competent Seneca Valley virus (NTX-010) by the pediatric preclinical testing program. *Pediatr. Blood Cancer* 55(2), 295–303 (2010).

19 Csatary LK, Gosztonyi G, Szeberenyi J *et al.* MTH-68/H oncolytic viral treatment in human high-grade gliomas. *J. Neurooncol.* 67(1–2), 83–93 (2004).

20 Wagner S, Csatary CM, Gosztonyi G *et al.* Combined treatment of pediatric high-grade glioma with the oncolytic viral strain MTH-68/H and oral valproic acid. *APMIS* 114(10), 731–743 (2006).

21 Freeman AI, Zakay-Rones Z, Gomori JM *et al.* Phase I/II trial of intravenous NDV-HUJ oncolytic virus in recurrent glioblastoma multiforme. *Mol. Ther.* 13(1), 221–228 (2006).

22 Hammill AM, Conner J, Cripe TP. Oncolytic virotherapy reaches adolescence. *Pediatr. Blood Cancer* 55(7), 1253–1263 (2010).

23 Radbill AE, Reddy AT, Markert JM *et al.* Effects of G207, a conditionally replication-competent oncolytic herpes simplex virus, on the developing mammalian brain. *J. Neurovirol.* 13(2), 118–129 (2007).

24 Friedman GK, Pressey JG, Reddy AT, Markert JM, Gillespie GY. Herpes simplex virus oncolytic therapy for pediatric malignancies. *Mol. Ther.* 17(7), 1125–1135 (2009).

25 Prestwich RJ, Harrington KJ, Pandha HS, Vile RG, Melcher AA, Errington F. Oncolytic viruses: a novel form of immunotherapy. *Expert Rev. Anticancer Ther.* 8(10), 1581–1588 (2008).