Oncolytic viruses (OVs) have been tested since the 1950s; however, it was not until the 1990s that viral genomic engineering resulted in the first generation of cancer-selective therapeutic OVs. These selective therapeutic OVs are designed to selectively replicate within tumor cells, sparing normal tissue, and eventually cause oncolysis. Further research has demonstrated a complex downstream effect from viral therapy. Beyond direct oncolytic effects, there has been more of a focus recently on the involvement of the innate and adaptive immunity. Recognizing the strong tumor-mediated immunosuppression of glioblastoma (GBM), OVs have secondary effects of developing adaptive immunity that can result in lasting antitumor effects.

Despite the promising nature of OVs, as discussed in this issue of Neurosurgical Focus, there are challenges in optimal delivery. Direct intratumoral delivery of viruses has been suboptimal due to backflow and limited viral distribution. However, in animal models, where delivery has been easier, successful cures have been achieved. Clearly, alternative delivery methods that distribute all of the viral dose widely throughout the tumor would be beneficial. Intraarterial (IA) delivery of OVs has been established in other cancers and has had early applications in GBM as well. In this review, we will discuss the unique applications of IA delivery of OVs, starting with concepts of OV, how they apply to IA delivery, and concluding with discussion of the current ongoing trials.

Intraarterial delivery of virotherapy for glioblastoma

Visish M. Srinivasan, MD,1 Frederick F. Lang, MD,2 and Peter Kan, MD3

1Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona; 2Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; and 3Department of Neurosurgery, University of Texas Medical Branch, Galveston, Texas

Oncolytic viruses (OVs) have been used in the treatment of cancer, in a focused manner, since the 1990s. These OVs have become popular in the treatment of several cancers but are only now gaining interest in the treatment of glioblastoma (GBM) in recent clinical trials. In this review, the authors discuss the unique applications of intraarterial (IA) delivery of OVs, starting with concepts of OV, how they apply to IA delivery, and concluding with discussion of the current ongoing trials. Several OVs have been used in the treatment of GBM, including specifically several modified adenoviruses. IA delivery of OVs has been performed in the hepatic circulation and is now being studied in the cerebral circulation to help enhance delivery and specificity. There are some interesting synergies with immunotherapy and IA delivery of OVs. Some of the shortcomings are discussed, specifically the systemic response to OVs and feasibility of treatment. Future studies can be performed in the preclinical setting to identify the ideal candidates for translation into clinical trials, as well as the nuances of this novel delivery method.

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Intravascular delivery of OV s has been performed. However, it is limited by the blood-brain barrier (BBB) and blood-tumor barrier (BTB), significantly limiting delivery and efficacy. Overcoming this limitation has been attempted by BBB disruption using mannitol to enhance IA delivery. One of the early uses of this for OV was described by Liu et al. in intracarotid delivery of an HSV vector (G47-delta) for breast cancer metastases to the brain.20 G47-delta spread in the mouse breast cancer model was assessed by X-gal staining, demonstrating good spread throughout the tumor with the BBB disruption. However, the virus was also noted to distribute to the liver and lung (other studies estimated 2.6%/g to the liver). Overall, these findings support the theory of IA delivery to enhance OV spread throughout the tumor, if the potential for systemic toxicity can be limited.

IA Virotherapy and Gene Therapy for Other Cancers

Hepatic Metastases

IA infusion of viruses has been clinically investigated for cancers other than GBM. Hepatic arterial infusion of a selectively replicating OV, dl1520 (Onyx-015), was performed in 2002 in a phase 2 trial by Reid et al.21 At that time, the enthusiasm around adenoviral therapies was limited by the contemporaneous report of a death from arterial infusion of an adenoviral gene therapy for ornithine transcarbamylase deficiency. For this application, they suggested the benefit of IA therapy for the diffuse/multifocal nature of recurrent hepatocellular carcinoma after surgery and radiation therapy. These same theoretical benefits apply to GBM as well. They used a combination therapy of hepatic IA infusion of live virus combined with 5-FU and leucovorin for gastrointestinal metastases to the liver. Their main finding was the ability to use a lower dose of live virus for safety (one-tenth of the dose used in the gene therapy trial), which was well tolerated. This induced a cyclical/recurrent viremia consistent with viral replication, proinflammatory cytokine induction, and evidence for chemosensitization of refractory tumors. In addition, this study was the first to demonstrate clinical replication of a therapeutic virus delivered by an IA route, with a subsequent rapid clearing of the virus from the blood. They concluded their paper with a goal of future studies to focus on “improving the efficiency of vascular delivery and on improving the replication and potency of the therapeutic virus.”

Head and Neck Cancer

Another area of clinical evaluation of OV s has been in head and neck cancer. In 2009, Xu et al.29 reported on a phase 1 clinical trial with AdV-tk/ganciclovir therapy in 18 patients with nasopharyngeal carcinoma. They demonstrated that AdV-tk gene therapy could be administered safely, although there were systemic symptoms (fever mostly) with systemic administration. They later wanted to translate this to treatment of high-grade gliomas. After demonstrating the intratumoral injection in the nasopharyngeal carcinoma, they followed this with an IA strategy to achieve dose intensification and localized, concentrated delivery. In 53 patients who underwent IA cerebral infu-
sion of AdV-tk, they achieved improved median progression-free survival (29.6 vs 8.4 weeks).

Additional gene therapy trials have been performed for head and neck cancer more recently as well. Li et al. reported in 2014 on 99 patients enrolled in a phase 3 randomized, placebo-controlled, double-blind trial, in which they found a better response with IA therapy (recombinant adenovirus−p53 [rAD-p53] gene therapy) with chemotherapy combined, rather than with each of the treatments alone with a placebo of the other. Furthermore, they confirmed the mechanistic success of this treatment: rAd-p53 treatment increased Bax expression in the primary tumor in 80% of the patients.

**Endovascular Selective Intraarterial Therapy**

ESIA therapy or infusion has been used to deliver therapeutic agents to brain tumors. This concept has been most successfully applied in retinoblastoma, but has also been evaluated in GBM. ESIA therapy of retinoblastoma is increasingly accepted as a treatment option over enucleation. It developed from the initial open surgical carotid infusion of triethyleneemelamine nitrogen mustard, to endovascular infusion of melphalan (t-phenylalanine mustard) into the internal carotid artery (ICA) with distal balloon occlusion, to now direct catheterization and infusion of melphalan, carboplatin, and topotecan through the ophthalmic artery, with a reported 92% ocular survival in 452 eyes.

Thus far, the therapeutic agent has been chemotherapy, including older agents such as cisplatin/vincristine, and more recently “newer” agents such as temozolomide and bevacizumab. These agents have had some limited success, but have not progressed beyond phase 2 studies. A therapy outside of the CNS (brachytherapy) has also been performed for another common oncological target. IA therapy has also performed for another common oncological target. IA therapy outside of the CNS (brachytherapy).

Other methods of using OVs can also be considered. Similar to conventional IA delivery, ESIA delivery can be performed with replication-selective viruses with therapeutic transgenes. ESIA delivery offers the advantage of increased specificity of delivery, especially if combined with MSCs. Although preclinical data are lacking thus far, these are areas of potential investigation. Examples of such therapeutic payload–carrying viruses that have been used for GBM include TOCA-24-RGD delivery to the gliomas; intracarotid delivery of free Delta-24 did not deposit into the virus, consistent with the non-BBB disruption arm of the Liu et al. study. The MSC–Delta-24 construct led to localization within gliomas, spread of Delta-24 into the glioma cells evenly throughout the tumor, and inhibition of xenograft growth with resultant improvement in mouse survival.

This preclinical work, as well as further studies that describe the mechanisms underlying MSC tropism for gliomas, established the concept of IA delivery. Intra- venous (IV) delivery is certainly easier from a clinical standpoint. However, studies of IV MSC delivery have been hampered by pulmonary passage, resulting in a marked reduction of the eventual MSC delivery at the target. Additionally, there have been concerns about the increased potential for neutralizing antibodies via IV administration, which can limit the effective dose of the virus and secondary immune response. Thus, MSCs provide “shielding” from the potential humoral antiviral response until the virus can be delivered to the tumor in high doses, in addition to its assistance in crossing the BBB (Table 1).

IA delivery of MSCs loaded with OVs (Delta-24) has been studied in an in vitro endovascular model as well as in a large animal canine model. These experiments have shown that IA microcatheter delivery of MSCs carrying OV retains the oncolytic effects of the virus as well as the tropism of the MSCs. Such delivery is quite robust, unaffected by various catheter factors (positioning SHAPE, infusion speed, or catheter type). When this method was performed in a canine model, it was found to be safe in the anterior circulation without dose-related toxicity. This is currently being evaluated in a phase 1 clinical trial of ESIA therapy with Delta-24 MSCs (www.clinicaltrials.gov no.: NCT03896568).

Other types of stem cells, including neural stem cells, have been considered and evaluated in animal models. However, MSCs are easier to harvest, can be used as either autologous or allogeneic types, have fewer ethical issues surrounding their use, and can easily be cultured in vitro.

Oncolytic HSV (oHSV) is another agent with potential for ESIA-MSC-OV therapy, as has been suggested by Shah. Whereas some clinical studies of oHSV used in the resection bed of GBMs resulted in “washout,” ESIA infusion with loading in MSCs and proapoptotic variant oHSV-TRAIL (tumor necrosis factor–related apoptosis-inducing ligand) may overcome these shortcomings.

Other methods of using OVs can also be considered. Similar to conventional IA delivery, ESIA delivery can be performed with replication-selective viruses with therapeutic transgenes. ESIA delivery offers the advantage of increased specificity of delivery, especially if combined with MSCs. Although preclinical data are lacking thus far, these are areas of potential investigation. Examples of such therapeutic payload–carrying viruses that have been used for GBM include TOCA-511 and TG6002, which carry cytosine deaminase– or 5-fluoro-uracil–producing genes, respectively. These have thus far been tested via IV infusion with follow-up oral administration.
Challenges in Immunotherapy

Both the promise of and the challenges for immunotherapy for GBM are related to the immunosuppressive environment, as GBM enables its proliferation by alteration of its microenvironment to support immune evasion. Tumor immunosuppression is mediated by transforming growth factor–β, vascular endothelial growth factor, prostaglandin E2, and interleukin (IL)–10, which results in T-cell depletion and suppression of T-cell cytotoxicity.39 Thus, the potential of activating the immune system by checkpoint inhibitors (CPIs) and other immunotherapies is promising.40 However, monotherapy with such therapies in the CNS, with its immune privilege, is less optimal as there is no activation stimulus. Thus, in the aftermath of the limited results of CPI monotherapy, there has been interest in combination therapy (discussed below). Challenges in designing and executing trials for a variety of immunotherapies have been reviewed extensively.41 These other challenges include modulation of the immune response, management of cerebral edema and dexamethasone, and minimizing immune-related adverse effects. Additional challenges include dynamic genetic mutation,42 heterogeneity,43 and changes over the course of treatment.44,45 Thus, treatments such as OV that are able to generate a lasting proimmune effect or have mechanisms independent of specific mutations are desirable.

Benefits of OV

There are several benefits to OV usage in GBM, some of which are particularly salient for IA or ESIA infusion compared to other agents. The first is selective replication; the selective nature of OVs allows a reduction in potential side effects as compared to IA delivery of chemotherapies, which may have diminished side effects intraarterially versus intravenously, but are still nonetheless active in the systemic circulation. ESIA delivery of OVs is theoretically ready for translation, given that other delivery mechanisms have shown some clinical value via intratumoral injection44 or CED. The establishment of clinical safety here is key, although ESIA OV trials still need to undergo phase
TABLE 1. Benefits and drawbacks of IA therapy of OVs for GBM

| Benefits                                      | Drawbacks                                                |
|-----------------------------------------------|----------------------------------------------------------|
| Minimally invasive delivery                   | Requires neurointervention expertise and inpatient setting; increased cost of delivery compared to IV delivery |
| Potential for repeat delivery                  | Repeat infusion still more involved compared to IV chemotherapy |
| Focused delivery of virus to tumor bed         |                                                          |
| Decreased systemic response                   |                                                          |
| Can be used in conjunction w/ MSCs to enhance delivery | May require “shielding” of virus from humoral antiviral factors |
| Opening of BBB to increase effective dose     |                                                          |

I testing to determine the maximum tolerated dose and unique safety of each agent. OVs generally target common and early mutations that affect nearly all tumor cells, such as p53 or retinoblastoma (Rb) mutations. This gives them efficacy against a host of tumors other than GBM, but also enables them to overcome the mutational heterogeneity that characterizes GBM.46

Tumor control via OV has been described in an early and late response.47 The use of MSCs in these cases as a carrier can also alter the response and immunological response in some ways. In the early response, there is direct tumor lysis by intracellular replication of OV. This can be enhanced by the addition of various moieties to the virus to enhance binding and affinity (e.g., the addition of RGD to the Delta-24 virus). The distribution of virus for this early phase can be theoretically enhanced by ESIA, also perhaps with the use of MSCs. The early phase is also characterized by tumor and MSC-mediated immunosuppression, which allows efficient viral replication. As this wears off, there is a late-phase response.13 This is characterized by antiviral leading to antitumoral immunity.47

The immune responses are elicited by pathogen-associated molecular patterns (PAMPs; e.g., viral capsid) and tumor milieu–associated molecular patterns. In this manner, the virus can essentially act as an active antitumor vaccine. GBM is known to have limited immunogenicity, with few known tumor-restricted antigens.41 This function of OVs in producing an immune response enables their effect as monotherapy as well as combination therapy (discussed later). This local inflammatory response is believed to then lead to adaptive antiviral and antitumoral immunity. These understood mechanisms of OV response need to be understood better in the context of a novel delivery method (IA/ESIA infusion), and then subsequently can be harnessed for the unique potential of this delivery (potentially, targeted/repeated infusions).

Potential for Combination Therapy

There is potential for combination therapies using ESIA infusion of OV, with other adjuncts such as traditional chemotherapy, CPIs, and/or radiation. Among these, there is some evidence to suggest that CPIs have some synergy with OVs. This can be extrapolated to include use with IA OV therapy.

CPIs for GBM, as studied recently in GBM with anti–PD-1 nivolumab,40 showed early promise but have been limited by the immunosuppressive environment of GBM. This might potentially be overcome by use of combination therapy.48 The concept is well described in a review by Jiang et al. (Fig. 2).49 The treatment choice between OV and CPI can be chosen based on the patient immune response and the immune checkpoint expression level. Combination therapy may be particularly helpful and/or required for patients with low-immunogenicity tumors (most GBMs), a weak cohort of Th1-primed lymphocytes, and high levels of expression of immune checkpoints in the tumor infiltrating T cells (Fig. 3).49 Many of the combination therapies discussed have theoretical advantages but still require preclinical validation.

CPIs have been used in combination therapy50 including with OVs.51 The goal here is to increase the immunogenicity of GBM. Currently, the only ongoing trial with OV-CPI is with DNX-2401 and pembrolizumab (www.clinicaltrials.gov no.: NCT02798406). Delta-24-RGD treatment for GL261 murine GBM was shown to change the recruitment of macrophages, NK cells, and CD4+ and CD8+ T cells to the tumor site.52–54 Thus, modification of the immune microenvironment by adenoviral therapy of high-grade gliomas can enhance the efficacy of immunotherapy, providing some preclinical basis for clinical testing of this combination therapy.

The use of combination therapies has been suggested in GBM to overcome tumor cross-resistance. When combination therapies use agents that have radically different mechanisms with limited overlapping toxicities, they are additionally likely to be tolerated and avoid resistance.21,55,56

Finally, IA infusion allows for easy repeat treatment with therapeutic OVs compared to alternative methods of delivery that require surgery (such as direct infusion and CED). Given the relative novelty of ESIA, this has not yet been studied, even in the preclinical arena. However, there is precedent for repeated IA treatment in retinoblastoma47 and in liver metastases.21,58 When used in a phase 2 clinical trial for gastrointestinal liver metastases, repeat infusion was found to have delayed secondary peaks of viremia, overcoming the presence of neutralizing antibody titers and antiviral cytokines (e.g., IL-6). Specific to the Delta-24-RGD, repeated intratumoral delivery has been found to have additional therapeutic value. Thus, it may theoretically help to extend the early-phase direct oncolytic effects of OVs, to be followed later by immune-mediated tumor clearance.

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Conclusions

Oncolytic virotherapy is a promising concept for treatment of malignant glioma and has already been used successfully in early clinical studies. IA therapy offers an alternative method of delivery of this selective virus into the tumor bed. Future studies can be performed in the preclinical setting to identify the ideal candidates for translation into clinical trials, as well as the nuances of this novel delivery method.

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Correspondence
Peter Kan: University of Texas Medical Branch, Galveston, TX. ptkan@utmb.edu.