

Oncolytic Viral Therapy of Glioblastoma: Will this Soon become a Reality?

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Editorial

The first oncolytic virus therapy (talimogene laherparepvec or T-VEC) in the U.S. was approved in October 2015 for the treatment of advanced melanoma patients [1]. Such novel and safer treatments are in active development but not yet available for brain tumors. Glioblastoma multiforme (GBM) is the most common and aggressive form of brain cancer in adults with median survival of less than 15 months [2]. Current radiotherapy and chemotherapy regimens not only have failed to significantly benefit high-grade tumor patients, but also are associated with severe long-term side effects that worsen the quality of life. The development of more effective and tumor-selective treatment modalities is urgently needed. In the last decade, oncolytic viruses (OV) have emerged as a potential cancer therapeutic agent. Ovs are replication-competent viruses that selectively infect and replicate in cancer cells harboring a multitude of genetic alterations that allows virus propagation. The virus then either directly disrupts tumor cells further releasing infectious virions, or indirectly stimulates the host's immune system to mount a sustainable anti-tumor response. Compared to conventional chemotherapy, advantages of OVs are two fold; 1) the incompetence of OVs to grow in normal cells due to intact anti-viral response and apoptotic pathways results in minimized side-effects, and 2) OVs self-amplify and the infection increases within and between tumor cells with time [3,4].

The clinical testing of oncolytic viruses to treat cancer began in 1950s, however, a stable tumor response was rarely observed and the treatment-related toxicity was a serious problem. This could be attributed to the use of impure viral preparations such as body fluids or tissue extracts from infected patients. The era of making safer OVs started in 1990s and since then nearly 400 articles have been published on glioma oncolytic virotherapy, and at least 8 different OVs have been investigated in about 20 clinical trials for the treatment of GBM patients alone [5].

In 1991, Martuza et al. created the first genetically engineered OV, a thymidine kinase (TK)-deficient herpes simplex virus (HSV-dlsptk), which showed potent tumor-killing efficacy in a murine model of glioblastoma [6]. This publication revived the field from a hiatus and since then a multitude of additional HSV mutants, HSV-1716, R3616, hR3, M032, G207, and G47Δ, have been generated. These modified strains present improved features such as safety, lower neurotoxicity, conditional tumor-selective replication, and high titer virus production. These mutants currently are at different stages in clinical trials (NCT00028158, NCT02062827, NCT02031965, NCT00157703) making HSV-1 the most extensively studied oncolytic virus in glioma therapy [7]. Adenovirus (Ad) is another extensively studied DNA virus for its oncolytic potential against glioblastoma in preclinical models and clinical trials. A tumor-selective conditional replication mutant of adenovirus carrying a deletion in the viral *E1B* gene (also known as ONYX-015) was tested in the phase 1 clinical trial for glioma patients

and the median survival of only 6.2 months was reported for all patients [8]. With a goal to simultaneously exploit receptor targeting and tumor-selective replication, adenovirus Delta24-RGD was developed. The mutation in the viral *E1A* gene restricts growth in cells with defective Rb pathway and the RGD moiety in the Ad fiber protein allows binding to selective integrins for cellular entry that are commonly overexpressed on tumor cells. The recombinant Delta24-RGD virus showed improved efficacy in preclinical models and is currently being investigated in phase 1/2 clinical trials (NCT01582516, NCT00805376). Many additional approaches to retarget adenovirus to tumor cells are in development and being studied in preclinical models [9].

The attenuated strains of poliovirus (PV), measles virus (MV) and vaccinia virus (VV) are used as vaccines on human beings, and these viruses also demonstrate strong oncolytic activity against tumor of different origin [5]. The RNA genome of the attenuated poliovirus type I (Sabin) vaccine was engineered to replace its IRES element with that of a nonpathogenic version from human rhinovirus type 2. This conditional tumor-selective poliovirus chimera (PVS-RIPO) fails to grow in normal cells, lacks poliomyelitis-like neurotoxicity and potently kills glioblastoma cells *in vitro* and *in vivo* models [10]. This virus was progressed to phase 1 trial against glioblastoma patients in 2011 (NCT01491893), and was granted a title of "breakthrough therapy" by the US FDA in May 2016. The Edmonston vaccine strain of measles virus is a safe and strong oncolytic virus that has been genetically modified to express carcinoembryonic antigen (*MV-CEA*) as a reporter gene to non-invasively monitor viral activity *in vivo* [11]. *MV-CEA* is being tested in an ongoing phase 1 clinical trial (NCT00390299) against glioblastoma from Mayo Clinic. Vaccinia virus, the vaccine agent for smallpox, is another human pathogenic virus with a strong anti-glioma oncolytic efficacy in preclinical models. The recombinant strain of VV with double deletions in the tyrosine kinase gene and the vaccinia growth factor gene (*vvDD*) has been developed and showed oncolytic efficacy and safety in murine and primate animal models [9]. Another strain of VV armed to express immunomodulatory human GM-CSF (*JX-594*) has prolonged survival in animal glioma models and has been tested in ongoing or completed clinical trials in patients with hepatocellular carcinoma and many other solid tumors (NCT00554372, NCT00429312, NCT00625456, NCT02630368) [5]. Certain viruses from non-human pathogenic background have also been recognized to possess oncolytic activity against human tumor cells. Newcastle disease virus (NDV), myxoma virus (*Myx*), vesicular stomatitis virus (*VSV*), parvovirus, Sindbis virus (*SIN*), and Seneca Valley virus (*SVV*) are few important members in this group. These viruses are actively being investigated for anti-glioma activity in preclinical models, and NDV and some other members have advanced for testing on human patients [5,9].

Clinical tolerability of high doses of OV (upto 10^{12} pfu) and the absence of OV treatment-associated death or severe adverse side effects have been the most remarkable observation from clinical trials. However, the therapeutic promises have not translated to bedside as significantly as it was shown in preclinical animal studies. Concerns over the use of OV as stand-alone therapy has been raised, and proposals of multimodal treatments using OV with immunotherapy/chemotherapy are in discussion [12]. Two clinical trials investigating the modified adenovirus DNX2401 with, 1) Temozolomide, a standard chemotherapeutic drug (NCT01956734), and 2) interferon gamma (IFN- γ), an immunomodulatory cytokine (NCT02197169), on glioblastoma patients are already in-progress. The tumor killing efficacy of OV depends on a fine balance between many factors including; 1) virus-mediated tumor cytolysis; 2) virus-induced host's anti-tumor immune response; and 3) innate/adaptive anti-viral response of the host's immune system. The key challenges remain in the areas of route of viral delivery (intratumoral, intravenous or intravascular), innate/adaptive anti-viral immunity and clearance of therapeutic virus from the body. To circumvent the issue of rapid virus clearance after intravenous delivery, ingenious ideas such as Trojan Horse technique have been tested and showed improved delivery in immuno-competent murine brain tumors models when neural stem cells or mesenchymal stem cells were used as Trojan Horse to carry the virus [13]. Also, the combination of oncolytic viruses with immunotherapeutic immune checkpoint inhibitors has potential to achieve durable clinical response. Finally, the possibility of cancer cells to develop resistance to any specific OV after long-exposure cannot be completely overlooked. The field is expanding with a growing list of new candidates and new collaborations between academic and pharmaceutical industries are expected to grow to develop advanced anti-GBM oncolytic viruses in coming years.

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