Oncolytic viruses: extreme treatment for an extreme disease

Balveen Kaur[†] *&*
E Antonio Chiocca

[†]*Author for correspondence*
The Ohio State University, Department of Neurological Surgery, Dardinger Laboratory of Neurosciences, OSUCCC, 385-D 410 West 12th Avenue, Columbus, OH 43210, USA
Tel.: +1 614 292 3984;
Fax: +1 614 688 4882;
balveen.kaur@osumc.edu
http://neurosurgery.osu.edu/Faculty/Kaur.htm

'The growth, spread and response to treatment of malignant cells from different tumors and even within a tumor display remarkable heterogeneity that seriously challenges effective therapy design and necessitates radical options to battle this radical disease.'

Cancerous cells violate the laws of cell cycle and senescence that govern growth and differentiation of normal cells. Decades of research have identified a multitude of molecular genetic alterations that are specific to neoplasia, and these are exploited to design targeted therapeutics. The growth, spread and response to treatment of malignant cells from different tumors and even within a tumor display remarkable heterogeneity that seriously challenges effective therapy design and necessitates radical options to battle this radical disease. One such treatment modality enlists the help of viral particles to selectively infect and specifically replicate in tumor cells, killing them in the process. The subsequent cycles of infection and replication by the released viral particles ultimately destroy the tumor. Both RNA and DNA viruses have been employed to generate such tumor-specific oncolytic viruses (OVs). Most OVs are genetically designed to be compromised in their capacity to replicate and/or evade host immune responses in normal cells. However, in most tumor cells, this deficiency permits viral replication and immune evasion. Viruses tested in clinical trials are derived from DNA viruses, such as adenoviruses, herpes simplex virus-1 and vaccinia virus, which have been engineered to display infection/replication potential specific to tumor cells [1]. There are also spontaneously arising or genetically engineered strains of RNA viruses, such as Newcastle disease virus, vesicular stomatitis virus, reovirus, poliovirus and Coxsackie virus, that can replicate selectively within tumors and are undergoing clinical testing as anticancer treatment modalities [2].

No clinical trial to date has reported significant side effects or toxicity that could be attributed directly to the administered virus, but evidence of efficacy has not been as forthcoming [1,3]. Detailed examination of the numerous possible reasons for the disappointing clinical response is crucial to maximize benefit from this treatment. The low toxicity and lack of adequate clinical response may reflect the current inability to produce clinical-grade virus in titers high enough to observe an antitumor response [4]. However, in principle, amplification of a single infectious viral particle should be sufficient to eradicate tumor cells after initial inoculation. This is evidenced by *in vitro* experiments wherein even very few particles of OV have displayed potent and selective lysis of neoplastic cells in tissue culture. Despite this, quite the opposite is noted *in vivo*, wherein viral titers in tumors decline after initial OV administration. Recent research from several laboratories has revealed the role played by innate immune defense mechanisms in the rapid clearance of therapeutic OV. Concordantly, transient suppression of innate host immune responses in animals results in increased propagation of virus and enhancement of OV therapy [5–7]. Paradoxically, accumulating evidence also suggests that OV-mediated oncolysis sets the stage for activation of a systemic adaptive immune surveillance that ultimately results in host rejection of cancer cells [8–10]. Detailed elucidation of the temporal pattern of the varied host responses after initial tumor infection is required before OV therapy can be fully exploited.

'OV-mediated oncolysis sets the stage for activation of a systemic adaptive immune surveillance.'

Solid tumors consist of neoplastic and stromal cells embedded in a complex extracellular matrix that comprises secreted matrix proteoglycans, proteases and secreted growth factors. Delivery of OVs by local intratumoral injection results in focal oncolysis and tumor necrosis, but the complex extracellular matrix may limit efficient spread of the virus throughout the tumor. Efforts to modify the tumor microenvironment to enhance spread of the virus to distal parts of the solid tumor would augment the virus's antitumor effectiveness. Consistent with this modification of the matrix, the use of bacterial collagenase to

10.2217/17460913.1.4.351 ISSN 1746-0913

degrade fibrillar collagen within the interstitium of the tumor has been shown to enhance viral spread and thereby enhance OV efficacy in a human melanoma xenograft in mice [11]. The ideal approach of systemic delivery of virus to increase dispersal throughout the tumor is limited by swift viral neutralization, degradation and clearance from the blood stream. A 'Trojan horse' approach that uses host cells to deliver an 'army' of viral particles to the site of malignant growth that are unseen by host immune responses is an exciting possibility that is currently being tested [12,13]. Mesenchymal progenitor cells (MPC) are a subpopulation of bone marrow stromal cells that can be isolated, expanded and then transduced *in vitro* with viral vectors and reintroduced with relative ease. Combined with their recently identified tumor-homing characteristics, these properties make MPCs an attractive vehicle for systemic distribution of OV [14]. Komarova and colleagues recently tested this approach for the systemic delivery of a genetically modified adenovirus and showed the feasibility of using virally loaded MPCs to efficiently target tumors with replication-competent viruses [12].

Considering the incredible complexity of human cancers, oncolytic viral therapy, and the elicited immune responses, it is highly unlikely that a single agent would translate effectively into cure. Hence, the future of cancer therapy lies in the strategic combination of therapeutic modalities that can enhance patient outcome synergistically. Changes in gene expression induced by ionizing radiation and post-translational modifications of cellular proteins can aid viral oncolytic therapy. The phenomenon of radiation-enhanced viral oncolysis is appealing, because the combined therapies are never antagonistic, and their combined activity ranges from additive to synergistic augmentation [15]. Treatment with chemotherapeutic agents, such as temozolomide and cisplatin, often leads to incomplete responses, partly due to the development of resistance by induction of DNA repair pathways. The induction of DNA repair pathways in the resistant cells provides a better environment for oncolysis and hence results in synergistic enhancement of oncolysis with chemotherapy [16,17]. Autologous bone marrow transplantation is often used after high-dose chemotherapy to limit toxicity. However, for several solid tumors, the presence of contaminating tumor cells (CTCs) within the allograft is thought to contribute to relapse. *Ex vivo* viral oncolysis to purge the autologous bone marrow transplant from contaminating CTCs may prove to be an attractive strategy to enhance the safety of high-dose chemotherapy [18].

'A 'Trojan horse' approach that uses host cells to deliver an 'army' of viral particles to the site of malignant growth...is an exciting possibility.'

The highly attenuated design of first-generation OVs tested clinically may be another factor contributing to the low efficacy observed in clinical trials. The design of next-generation viruses incorporates ways to make OVs more potent without compromising safety.

Future OVs are being 'dually armed' to destroy cancers directly and by adjuvant delivery of therapeutic/cytotoxic genes. Comparing transgene expression through replication-competent and -incompetent vectors has shown the former to last longer and cover a more extensive area after infection [19]. Therapeutic genes delivered by OV include antineoplastic genes, such as antiangiogenic factors targeting tumor vasculature, cytokines to activate immune-mediated tumor killing, and prodrug-activating enzymes to enhance tumor cytotoxicity [20,21]. Such cancer terminator viruses facilitate replication of cancer-sensitive viruses and robust expression of transgenes that allow maximum lysis of tumor cells [22].

The restricted expression of receptors that facilitate viral infection has also seriously limited the success of virus-mediated oncolysis. For example, the low-level expression of adenovirus receptor, CAR, on most cancer cells seriously limits the ability of adenovirus-based vectors to infect a wide range of tumor cells. Recombinant viruses genetically modified to infect tumor tissue through heterologous pathways have been generated, establishing the feasibility of retargeting viral infection. The same may well hold true even for other, more widely infectable viruses.

The design of future OVs incorporates strategies to increase the potency and selectivity of viruses so that cytotoxicity is increased and toxicity is minimized. Virulent viral genes (originally deleted in first-generation viruses) are reintroduced under the governance of tumor- or tissue-specific transcription factors to govern viral virulence in a tumor-/tissue-specific fashion. This strategy has also been harvested to target cancer stem cells using promoters of genes expressed in stem cells to drive viral virulence [23].

The myriad of approaches being investigated for OV therapy highlights the strong faith of numerous investigators and clinicians in this treatment modality. However, it has become increasingly evident that the war against cancer will not be won by a single treatment strategy, but requires the pooling of the research resources of the different pharmaceutical companies and private and academic investigators committed to this cause.

Bibliography

1. Cutter JL, Kurozumi K, Chiocca EA, Kaur B: Gene therapeutics: the future of brain tumor therapy? *Expert Rev. Anticancer Ther*. 6(7), 1053–1064 (2006).
2. Aghi M, Martuza RL: Oncolytic viral therapies – the clinical experience. *Oncogene* 24, 7802–7816 (2005).
3. Jiang H, McCormick F, Lang FF *et al.*: Oncolytic adenoviruses as antiglioma agents. *Expert Rev. Anticancer Ther.* 6(5), 697–708 (2006).
4. McCormick F: Future prospects for oncolytic therapy. *Oncogene* 24, 7817–7819 (2005).
5. Abordo-Adesida E, Follenzi A, Barcia C *et al.*: Stability of lentiviral vector-mediated transgene expression in the brain in the presence of systemic antivector immune responses. *Hum. Gene. Ther.* 16, 741–751 (2005).
6. Balachandran S, Thomas E, Barber GN: A FADD-dependent innate immune mechanism in mammalian cells. *Nature* 432, 401–405 (2004).
7. Fulci G, Breymann L, Gianni D *et al.*: Cyclophosphamide enhances glioma virotherapy by inhibiting innate immune responses. *Proc. Natl Acad. Sci. USA* 103, 12873–12878 (2006).
8. Andreansky S, He B, van Cott J *et al.*: Treatment of intracranial gliomas in immunocompetent mice using herpes simplex viruses that express murine interleukins. *Gene Ther.* 5, 121–130 (1998).
9. Bennett JJ, Malhotra S, Wong RJ *et al.*: Interleukin 12 secretion enhances antitumor efficacy of oncolytic herpes simplex viral therapy for colorectal cancer. *Ann. Surg.* 233, 819–826 (2001).
10. Todo T, Martuza RL, Dallman MJ, Rabkin S: *In situ* expression of soluble B7-1 in the context of oncolytic herpes simplex virus induces potent antitumor immunity. *Cancer Res.* 61, 153–161 (2001).
11. McKee TD, Grandi P, Mok W *et al.*: Degradation of fibrillar collagen in a human melanoma xenograft improves the efficacy of an oncolytic herpes simplex virus vector. *Cancer Res.* 66, 2509–2513 (2006).
12. Komarova S, Kawakami Y, Stoff-Khalili MA, Curiel DT, Pereboeva L: Mesenchymal progenitor cells as cellular vehicles for delivery of oncolytic adenoviruses. *Mol. Cancer Ther.* 5, 755–766 (2006).
13. Raykov Z, Balboni G, Aprahamian M, Rommelaere J: Carrier cell-mediated delivery of oncolytic parvoviruses for targeting metastases. *Int. J. Cancer* 109, 742–749 (2004).
14. Nakamizo A, Marini F, Amano T *et al.*: Human bone marrow-derived mesenchymal stem cells in the treatment of gliomas. *Cancer Res.* 65, 3307–3318 (2005).
15. Advani SJ, Mezhir JJ, Roizman B, Weichselbaum RR: ReVOLT: radiation-enhanced viral oncolytic therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 66, 637–646 (2006).
16. Adusumilli PS, Chan MK, Chun YS *et al.*: Cisplatin-induced GADD34 upregulation potentiates oncolytic viral therapy in the treatment of malignant pleural mesothelioma. *Cancer Biol. Ther*. 5, 48–53 (2006).
17. Aghi M, Rabkin S, Martuza RL: Effect of chemotherapy-induced DNA repair on oncolytic herpes simplex viral replication. *J. Natl Cancer Inst.* 98, 38–50 (2006).
18. Thirukkumaran CM, Luider JM, Stewart DA *et al.*: Reovirus oncolysis as a novel purging strategy for autologous stem cell transplantation. *Blood* 102, 377–387 (2003).
19. Ichikawa T, Chiocca EA: Comparative analyses of transgene delivery and expression in tumors inoculated with a replication-conditional or -defective viral vector. *Cancer Res.* 61, 5336–5339 (2001).
20. Dalba C, Klatzmann D, Logg CR, Kasahara N: Beyond oncolytic virotherapy: replication-competent retrovirus vectors for selective and stable transduction of tumors. *Curr. Gene Ther.* 5, 655–667 (2005).
21. Mullen JT, Kasuya H, Yoon SS *et al.*: Regulation of herpes simplex virus 1 replication using tumor-associated promoters. *Ann. Surg.* 236, 502–512; discussion 502–512 (2002).
22. Sarkar D, Su ZZ, Fisher PB: Unique conditionally replication competent bipartite adenoviruses-cancer terminator viruses (CTV): efficacious reagents for cancer gene therapy. *Cell Cycle* 5, 1531–1536 (2006).
23. Kambara H, Okano H, Chiocca EA, Saeki Y: An oncolytic HSV-1 mutant expressing ICP34.5 under control of a nestin promoter increases survival of animals even when symptomatic from a brain tumor. *Cancer Res.* 65, 2832–2839 (2005).

Affiliations

- *Balveen Kaur*
  The Ohio State University, Department of Neurological Surgery, Dardinger Laboratory of Neurosciences, OSUCCC, 385-D 410 West 12th Avenue, Columbus, OH 43210, USA
  Tel.: +1 614 292 3984;
  Fax: +1 614 688 4882;
  balveen.kaur@osumc.edu
  http://neurosurgery.osu.edu/Faculty/Kaur.htm
- *E Antonio Chiocca*
  James Cancer Hospital and Solove Research Institute, The Ohio State University Medical Center, N-1017 Doan Hall, 410 West, 12th Avenue, Columbus, OH 43210, USA
  Tel.: +1 614 293 5444;
  Fax: +1 614 293 4281;
  ea.chiocca@osumc.edu