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Commentary on oncolytic viruses: past, present, and future

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ABSTRACT

Whither oncolytic viruses? From the peak of their popularity in the early 2000s, when the ONYX-015 adenovirus had just entered the clinic, and then again in 2015 when the Food and Drug Administration-approved talimogene laherparepvec (also known as OncoVEX^{GM-CSF}), which briefly revived interest, oncolytic viruses (OVs) have mostly fallen out of favor despite the many pharmaceutical companies with OVs in development.

This commentary enumerates and addresses the core conceptions, perceptions, and misconceptions that characterize the current 'trough of disillusionment' in which the field of anticancer virotherapy finds itself and suggests reasons for optimism.

PERCEPTION #1: ONCOLYTIC VIRUSES DO NOT TREAT DISTANT LESIONS

To put this claim in better context, radiation therapy is also a local therapy, which up to 50% of patients with cancer receive at some point in their treatment trajectory. Depending on the scientific author consulted, radiation therapy, like oncolytic virotherapy, may or may not induce abscopal ('ab'-away; 'scopus'-target) antitumor responses, and even if they do, it is only rarely or sporadically.[1]

The fact is that however effectively oncolytic viruses lyse or destroy cancer cells in situ, their immunological effect is decidedly ex situ—somewhat analogous to an intradermally or intramuscularly administered vaccine that protects, for example, the distantly located lungs from pneumonia through induction of paraimmunity. An issue is how best to optimize the intrinsic vaccine-like activity of oncolytic viruses so that cellular immunity more effectively targets the non-injected metastatic lesions. Systemic immunization in cancer is especially difficult because it requires that a cytotoxic T lymphocyte (CTL) response develop from local injection, and that this response is effective enough to infiltrate and eradicate other lesions, despite all the suppressive barriers that are present, including fibrosis, poor perfusion, programmed death-1 (PD-1)-programmed cell death ligand 1 checkpoints, and myeloid-derived suppressive cells.

That said, talimogene laherparepvec (T-VEC) has demonstrated evidence of abscopal activity.[2] Also, in a soon-to-be published 26-patient phase I trial[3] with intratumorally (IT) injected AdAPT-001, an attenuated adenovirus that expresses a transforming growth factor-beta (TGF-β) trap, with which the authors are closely associated, 2 patients had partial responses, and 5 patients had durable stable disease beyond 6 months. Furthermore, these patients with advanced cancer demonstrated pseudoprogression of injected and uninjected lesions, that is, transient enlargement as shown in panel 3 of figure 1 followed by tumor regression or response. See figure 2 for further evidence of abscopal activity of AdAPT-001.

However, putting aside for the moment this issue of abscopal effects, and their consistency or lack thereof, OVs are conceptually well suited for local delivery in a single tumor prior to surgical resection. In a 75-patient phase II neoadjuvant trial of T-VEC plus surgery versus surgery alone, the 5-year relapse-free survival rate was 22.3% with T-VEC plus surgery, compared with 15.2% for surgery alone (HR 0.76; 80% CI 0.60 to 0.97). The 5-year survival rate of patients treated with T-VEC prior to surgery was 77.3% compared with 62.7% with surgery alone (HR 0.54; 80% CI 0.36 to 0.81).[4]

PERCEPTION #2: ONCOLYTIC VIROTHERAPY IS UNSUITABLE FOR SYSTEMIC DELIVERY DUE TO IMMUNE ELIMINATION

To be sure, the presence of neutralizing antibodies (NAbs) limits or prevents intravenous administration of OVs like adenovirus, coxsackievirus, Newcastle disease virus, polio, herpes, measles, vesicular stomatitis virus, and vaccinia. However, this statement comes with at least four qualifications.

The first is that Reid *et al* successfully administered ONYX-015 through the hepatic artery to patients with gastrointestinal carcinoma metastatic to the liver in phase I and II trials.[5] These trials witnessed significant tumor

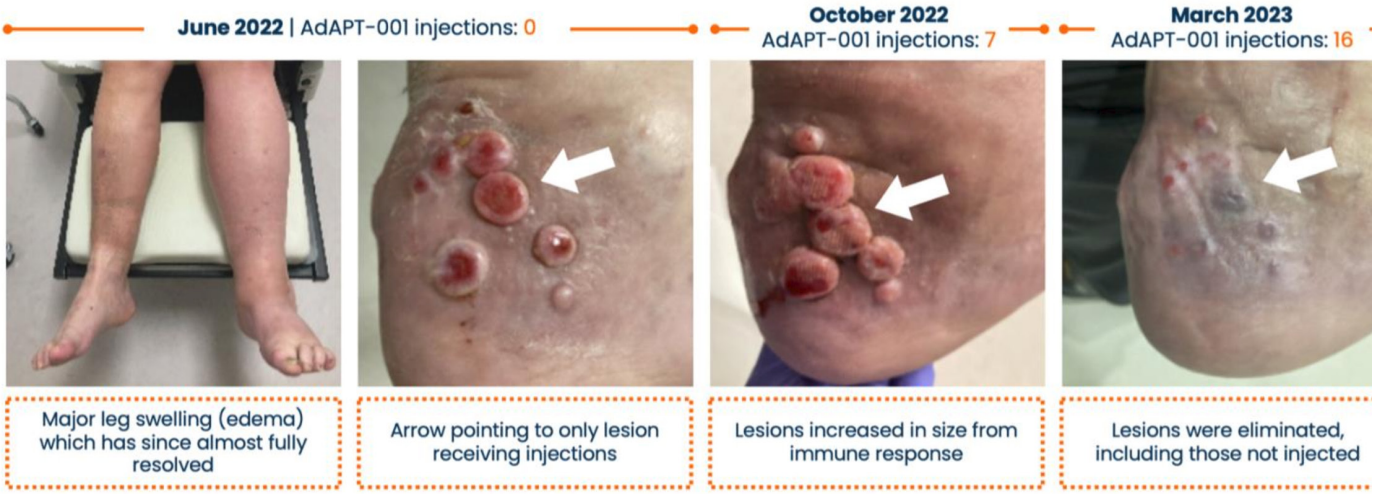

Figure 1 Patient with eccrine adenocarcinoma with near-complete resolution of heel tumors after single agent AdAPT-001 injection every 2 weeks.

responses despite the presence of NAbs likely because the kinetics and stoichiometry of antibody neutralization through the hepatic artery are insufficient to clear the high concentration of locally administered OVs before they reach target tumor cells. Likewise, NV1020, an attenuated derivative of wild-type Herpes Simplex Virus Type 1 (HSV-1), has been given successfully by hepatic artery infusion for the treatment of liver metastases.[6]

Also, the oncolytic herpes virus, HSV1716, has been given intravenously to pediatric patients in a phase I clinical trial. However, viremia was only seen after the first dose, confirming systemic exposure, but not on subsequent doses after antiviral immunity developed.[7]

The second is that liposomal encapsulation of the OV may shield it from antibody neutralization during intravenous administration, and boost local and systemic

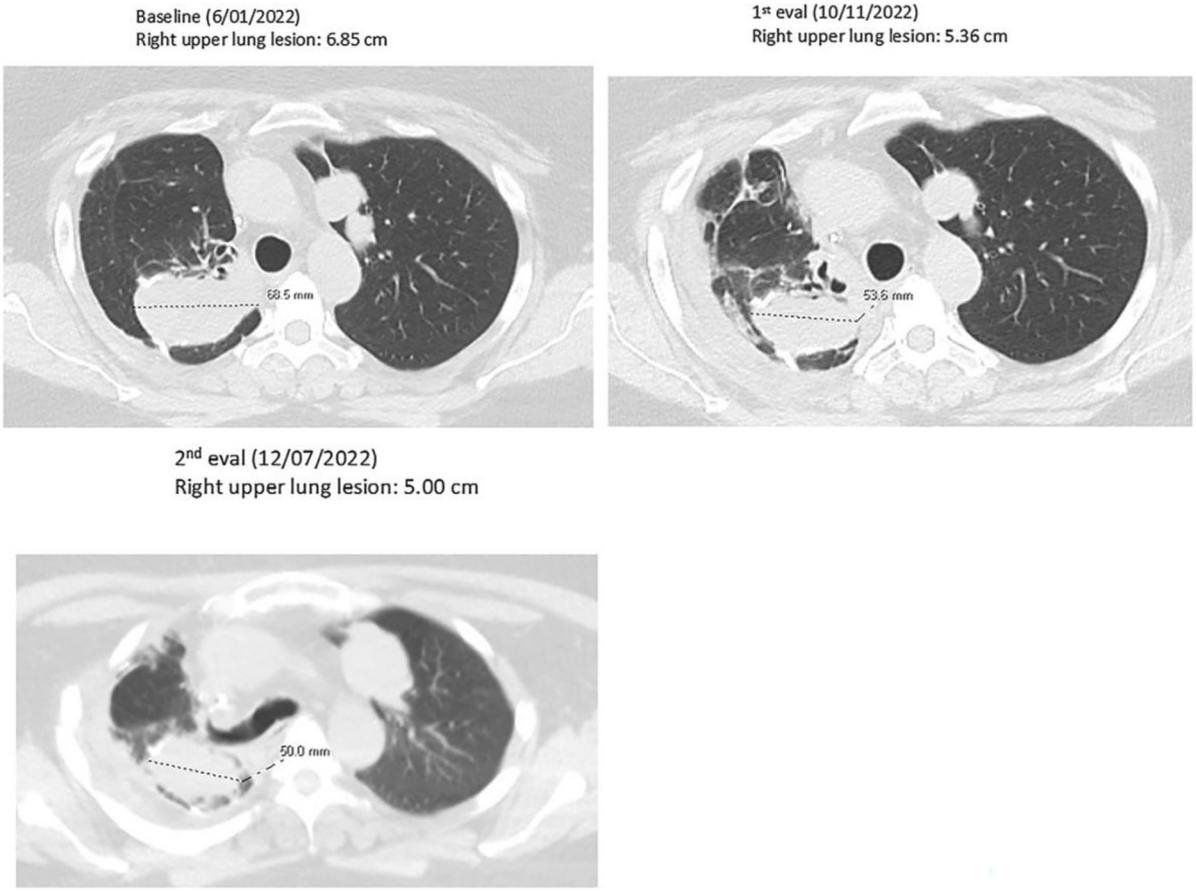

Figure 2 Evidence of distant shrinkage of a leiomyosarcoma metastatic lung lesion after local injection of AdAPT-001 in a subcutaneous abdominal lesion.

anticancer activity possibly due to more efficient accumulation from an enhanced permeability and retention effect, as certain preclinical studies suggest.[8]

The third is that the intravenous route is possible with some viruses that are not endemic and where human exposure is limited, such as for rhabdovirus and some strains of coxsackievirus and adenovirus.

PERCEPTION #3: THE PRESENCE OF NEUTRALIZING ANTIBODIES BLOCKS ANTITUMOR ACTIVITY EVEN IN INJECTED TUMORS

This is a misconception. Neutralizing antibodies do not decrease the efficacy of local administration, as evidenced by the fact that tumors treated with the oncolytic adenoviruses ONYX-015[5] or AdAPT-001[9] initially remained stable or demonstrated pseudoprogression before ultimately responding months later, well after neutralizing antibodies would have been induced or boosted. Also, as one of the reviewers of this manuscript pointed out, T-VEC is initially given at a low dose for seroconversion prior to the administration of higher doses. Plus, the induction of immune responses against the virus may reduce immunosuppression and augment the antitumor effect.

PERCEPTION #4: COMBINATION WITH IMMUNE CHECKPOINTS HAS BEEN EQUIVOCAL

An open question in oncology is what to combine checkpoint inhibitors with so that more patients benefit, regardless of tumor type.

The combination with oncolytic viruses such as T-VEC has so far met with limited success. In a 660-patient phase III advanced unresectable melanoma trial called KEYNOTE-034 (NCT02263508), the combination of T-VEC plus pembrolizumab failed to significantly improve the progression-free survival and overall survival (OS) primary end points over placebo and pembrolizumab.[10] However, in a prior phase Ib/II randomized 198-patient advanced melanoma study trial, the ORR of T-VEC plus ipilimumab was significantly better than ipilimumab alone (p=0.033).

This inconsistent efficacy with T-VEC (and other IT-injected oncolytic viruses like the adenovirus, DNX-2401, which increased OS but not response rates in a 49-patient phase I/II study in recurrent glioblastoma)[11] is possibly related to the choice of tumor type, in this case melanoma, which is already immunologically hot and, therefore, potentially less likely to respond to an oncolytic virus, whose main mechanism of action likely involves transformation of cold tumors into hot ones. It is also possibly related to the different checkpoint inhibitors used, as anti-PD-1 and anti-CTL-associated protein 4 act differently.

Another contributing factor almost certainly relates to operator-dependent variability, and to the quality of in situ delivery. A key often overlooked technical aspect of intratumoral injection is the considerable amount of infusate that is lost due to backflow from the injection site if careful attention is not paid to the choice and size of tumor, placement of the needle, and the injection technique itself. Proper technique involves insertion of the needle in the tumor, bevel upwards, after which the infusate is injected slowly and evenly while the provider moves the needle in a fan-shaped pattern. This technique, however, is difficult to standardize, requires training, and depends, to a greater or lesser extent, on the competency/clinical judgment of the healthcare provider.

The larger the trial, and the more clinical sites and providers that are involved, the harder it is to minimize technical variability, and the greater the likelihood of suboptimal delivery, which may partly account for the failure to replicate the success with T-VEC in the much larger phase III.

But, regardless of the operator or the technique used, single needle injection only reaches a small fraction of the total tumor, which is the reason to consider multineedle injection for more efficient and less error prone OV delivery.

PERCEPTION #5: ELEVATED INTERSTITIAL PRESSURES AND A DENSE TUMOR EXTRACELLULAR MATRIX HINDER VIRAL SPREAD DURING LOCAL INJECTION

The dense extracellular matrix (ECM) and high interstitial pressures that are present indeed constitute barriers to intratumoral oncolytic viral spread. Under investigation are the use of matrix-degrading enzymes like collagenase or hyaluronidase and antivascular endothelial growth factor agents to attenuate the vascular leakiness. The TGF-β trap that AdAPT-001 expresses inhibits the profibrotic, and pro-angiogenic cytokine, TGF-β,[12] and so it may also contribute to more efficient viral spread.

PERCEPTION #6: ONCOLYTIC VIRUSES ARE OVERATTENUATED AND OVERMODIFIED AND TRANSGENES LIKE GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR ARE REDUNDANT

It is true that 'overengineering' and 'overmodification' of oncolytic viruses for better safety and tumor selectivity potentially comes at the expense of potency and replication efficiency. It is also true that transgenes like granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-alpha, are potentially redundant since these cytokines are already produced at high levels in response to viral infections.[13]

In contrast to many other OVs, AdAPT-001 is minimally modified for near wild-type levels of replication in tumor cells. Plus, the TGF-β trap that AdAPT-001 expresses is nonredundant since it is not a naturally occurring protein.[14]

Finally, since any modification of oncolytic viruses potentially attenuates their fitness and cytotoxicity, it follows that the insertion of transgenes is not necessarily required or even desired, as the transgene-less oncolytic viruses, HSV-1G47Δ and DNX-201, which still mediate antitumor activity, illustrate.[15 16]

PERCEPTION #7: ONCOLYTIC VIRUSES ARE TOO LABOR-INTENSIVE AND EXPENSIVE TO MANUFACTURE

Historically, production of viral vectors at scale was prohibitively time-consuming and expensive but that is

no longer the case with the development of serum-free suspension cell culture.

So, to conclude, whither oncolytic viruses and what of their future? Will they follow a typical 'hype cycle' pattern in which a trough of disappointment ('bust') follows an initial peak of enthusiasm ('boom') when expectations are not met and culminates with revitalization, reputational recovery, and, ultimately, success in the form of more regulatory approvals ('re-boom')? To quote an old Danish proverb, 'making predictions is hard, especially about the future'.

From our perspective, however, oncolytic viruses are already on the upward slope of the curve, thanks to better designed viral vectors with more effective immunostimulatory transgenes that promise to drive increased abscopal activity, cheaper and less cumbersome manufacturing practices, and the possibility to bypass the technical difficulties of intratumoral injection with liposomal encapsulation and/or intra-arterial administration.

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