Oncolytic Virotherapy Needs Trials, Not Access Programs

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Running Title: Oncolytic Virotherapy Trials

Conflicts of Interest: Kevin Harrington has received research funding from Oncolytics Biotech Inc., Genelux GmbH and Oncos Therapeutics.

Summary

Oncolytic virotherapy is a novel treatment for cancer that exerts direct lytic and indirect immune-mediated anti-tumor effects. A Finnish research team has reported on an advanced therapy access program for oncolytic adenovirus. The strengths and weaknesses of this approach are highlighted with a view to informing future study conduct.

Word Count = 49
In this issue of Clinical Cancer Research, Kanerva et al report data on their use of a range of oncolytic adenoviruses in patients with a variety of different tumor types [1]. Their results represent an important addition to the literature in the area and highlight an interesting philosophy towards clinical testing of novel biological agents. Analysis of their data will be instructive to those working in this emerging field.

For the last decade, the mainstream of clinical research in oncolytic virotherapy has been dominated by studies which have followed the classical drug development paradigm. Accordingly, a relatively small number of candidate viruses have entered phase I dose-escalation studies which established safety and defined recommended phase II doses which have subsequently been tested for efficacy in specific tumor types. Although this approach has been relatively slow, it has been successful – resulting in randomised phase III studies of talimogene laherperepvec (T-Vec, Amgen Inc.) in melanoma [2,3] and pelareorep (Reolysin, Oncolytics Biotech. Inc.) in head and neck cancer [4,5] and a randomised phase II study of pexastimogene devacirepvec (JX-594, Jennerex Biotherapeutics) in hepatocellular cancer [6]. As a consequence of this careful stepwise approach to clinical trials, there is increasing interest in the use of oncolytic viral agents and a genuine sense that they have the potential to become licensed anti-cancer therapeutics.

Against this conventional background, it is, therefore, interesting to review data generated by the research group led by Akseli Hemminki and colleagues in Helsinki, Finland. Hemminki’s team have taken an entirely different approach to developing oncolytic adenoviruses. Under the terms of a European directive (EU hospital exemption, article 28 of Regulation 1394/2007/EC), this group was permitted to pursue an Advanced Therapy Access Program (ATAP) (ISRCTN10141600) in which they delivered “personalized virus therapy for individual cancer patients with refractory solid tumours.” In practical terms, this gave the team licence to administer “treatment with oncolytic viruses where the virus type, dose, dosing regimen, virus sensitizers, combination therapies and route of injection is optimized for each individual” [7]. Critically, patients enrolled in this program were not treated as part of a conventional clinical trial. As a result, treating physicians had significant flexibility and patients (including those with pediatric tumours) were able to receive intratumoural injections of one or more of up to six different adenoviruses with or without concomitant low-dose cyclophosphamide (given for its putative immunomodulatory effects in the context of virotherapy). Some patients received “single” treatments – defined rather curiously as fewer than three injections in a period of ten weeks – while others had “serial” treatments. The choice of virus and the strategy for switching between the six adenoviruses included in the program appears to have been unsystematic, although the vast majority of treatments were delivered with one of three granulocyte-macrophage colony-stimulating-factor (GM-CSF)-expressing viruses. A mere handful of treatments were delivered with three non-GM-CSF-expressing adenoviruses (ICOVIR-7, Ad5/3-Cox2L-d24, Ad3-hTERT-
E1), making it extremely difficult to draw any strong conclusions about their contribution to the program.

Having treated more than 100 patients in their program, it is telling to note that Hemminki’s team has now re-entered the mainstream and is conducting a standard dose-escalation study of their lead agent CGTG-102 (Ad5/3-D24-GMCSF) in patients with refractory cancers [8]. Nonetheless, and to their considerable credit, the group continues to present data from their completed ATAP studies which provide insights that might not be possible within the relatively narrow confines of a standard phase I/II trial design. So, what lessons can we learn from the ATAP experiment and how can we use this information to shape future trial design for oncolytic virotherapy?

The first and least surprising finding was that oncolytic adenoviruses were safe when administered by single or serial intratumoural injections at doses up to $4 \times 10^{12}$ virus particles. This safety signal, which emerged without a formal dose-escalation design, mirrors experience with other oncolytic viruses, even those that have been delivered intravenously. The authors’ extensive use of low-dose cyclophosphamide without an evident increase in virally-induced toxicity was reassuring, but the current report must be seen as a missed opportunity adequately to define the immunological effects of this approach in the clinic. Were regulatory T cells (or other subpopulations) affected in the expected manner and did cyclophosphamide blunt the anti-viral antibody response? Certainly, it is reasonable to suppose that answers to such questions would have been more likely to emerge from a conventionally rigorous trial protocol.

The group’s experience of delivering different adenoviruses as part of a “sero-switching” approach to abrogate the generation of neutralising anti-viral antibodies was adventurous and potentially important. They previously reported the effect of capsid switching using Ad5, Ad5-RGD and Ad5/3 adenoviruses in 24 patients, but in that study no clear systematic strategy for capsid switching could be discerned and virus was administered by various routes (intravenous, intratumoral and intracavitary), even in the same patient [9]. Unfortunately, even though all patients in the current report received intratumoural injections, once again there appeared to be no pre-determined strategy for introducing different viruses and this brings into question the validity of some of the authors’ conclusions about the relative importance of effective tumor infection versus enhanced immunogenicity. In addition, it is regrettable that the authors did not report anti-adenoviral neutralising antibody levels in this relatively homogeneous group of patients who did and did not undergo “sero-switching”. Such data would be an invaluable addition to the literature.

Perhaps the greatest strengths and weaknesses of the current report lie in the interpretation of the immunological analyses of single and serial adenovirus treatments. The authors measured T cell frequencies in the blood and categorised the data as showing “induction, trafficking or anergy”. Without doubt, most would not
argue with their view that inducing an increased number of total and tumor antigen-specific CD8+ T cells in the circulation might indicate a situation favoring anti-tumor efficacy. Furthermore, the correlation between anti-tumor and anti-viral T cell responses following treatment with CGTG-102 appeared robust and highly suggestive of virally-induced anti-tumor epitope spreading (Figure 1). Collectively, these data represent a major contribution to the research field. In direct contrast, the suggestion that a fall in circulating (total or specific) T cells should be called “trafficking” must be viewed with extreme caution – especially if the reader is invited to suppose that the T cells may be trafficking to the tumor. In the absence of sequential biopsies demonstrating intratumoral T cell accumulation following virus injection, those data should be viewed as nothing other than hypothesis-generating.

Therefore, despite a number of considerable strengths, the overall impression left by this work is disappointing. Ultimately, it would appear that, by allowing physicians flexibility in treatment delivery and by including large numbers of patients who did not contribute to all of the safety, efficacy and biological endpoints, this brave experiment failed to deliver definitive results. In future, the development of oncolytic virotherapy must continue to rely on carefully designed clinical trials, rather than access programs.

WORDS = 1143

Figure 1. Local adenoviral administration mediates both direct and immune-mediated anti-tumour effects. 1. Adenovirus is administered by intratumoral injection. 2. Virus infects tumor cells. 3. Virus replicates in tumor cell and causes productive infection with subsequent infection of neighboring cells. 4. Tumor cell lysis (dashed membrane of infected cell) releases viral and tumor-associated antigens and virally-expressed GM-CSF. 5. Antigen-presenting (dendritic) cells are attracted to the site of virally-induced tumor cell lysis and GM-CSF release and phagocytose viral (more abundant) and tumor antigens. 6. Dendritic cells migrate to lymph node and spleen and present antigens to virus- and tumor-specific T cells. 7. Specific T cells are induced and are released to the circulation. 8. Circulating virus- and tumor-specific T cells are detected in the circulation. 9. T cells traffic to the tumor. 10. Virus-specific T cells kill virally infected tumor cells. 11. Tumor-specific T cells kill tumor-antigen expressing tumor cells.
References


Figure 1:

1. Viral antigen
2. Virally-expressed GM-CSF
3. Tumor-associated antigen
4. Anti-viral T cell
5. Anti-tumoral T cell
6. Adenovirus

Tumor cells

Dendritic cells

Blood vessel

Node

Spleen

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Published OnlineFirst April 2, 2013.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-0571

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