Oncolytic Virotherapy Trials—Letter

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We would like to thank Prof. Harrington for his insightful commentary (1) regarding our article by Kanerva and colleagues (2). During 2007–2011, the Advanced Therapy Access Program (ATAP) provided a unique opportunity for patients to access a technology they would not otherwise have had access to, as no oncolytic virus trials were ongoing at the time in Finland. This program was one of the few or possibly the only attempt thus far to take advantage of the EU Advanced Therapy Directive (1394/2007/EC), which defines the rules for individualized patient-by-patient treatment under the “Hospital exemption.” This Directive requires patients to be treated in an individually tailored manner, under the sole responsibility of the treating physician, thus by definition resulting in heterogeneity.

However, as mentioned by Prof. Harrington, one can perhaps learn from these treatments. Just like a surgeon improves his skills by operating, a gene therapist may understand his tools better by using them. The EU Directive requires national bodies to regulate these personalized treatments. In Finland, the regulatory body requires a production permit, reporting on safety and adverse events (both immediate and delayed, if present), and they also require the risk:benefit ratio of the treatments to be analyzed and reported. Optimizing the treatment for each patient and being able to evaluate risk:benefit require quite a comprehensive set of assays but this is not unusual in concurrent oncology; an increasing number of analyses are used in routine practice to individualize treatments for each patient.

A key difference between trials and treatments is that in the latter, interventions cannot be conducted for scientific reasons. Only samples relevant for the patient can be collected. As the World Medical Association Declaration of Helsinki article 35 requires physicians to report data from all experimental therapies, and not just trials, the legal interpretation has been that data from ATAP should also be reported. However, it should be noted that ATAP reports do not constitute prospectively planned series of patients treated according to a predefined protocol. Instead, the manuscripts could be categorized as retrospective case series.

Prof. Harrington asks what lessons can be learned from ATAP. Keeping in mind that the only goal of personalized therapy can be to help the patient, not gather scientific data, can ATAP nevertheless help science move forward? He points out that the safety of the treatments seems convincing. However, he would like to see more data on the immunologic effect of cyclophosphamide. Although we agree that a more detailed examination of this question would be interesting, we would like to refer to the article by Cerullo and colleagues, where 3 different cyclophosphamide schedules were reported, including some immunologic analyses (3).

The suggestion of looking at neutralizing antibodies in the patients reported in the study by Kanerva and colleagues (2) was an excellent one. To complement data published earlier (4, 5), we have reported some new data here in Table 1 (patient data are published with ethics committee permission). All serial treatment patients (i.e., patients who received 3 virus injections) from Kanerva and colleagues (2) from whom neutralizing antibody titers were available are shown. Antibodies were induced in all patients and there was not much difference if a virus was given once or twice; both median titers were 1,024. However, confirming our previous data (5), 3 to 5 weeks after the first treatment with an oncolytic adenovirus, just before the second injection, there was a smaller neutralizing titer against the capsid used in the second treatment, even if the capsid modifications were slight. At baseline for the second virus injection in the “seroswitch” serial treatment patients, the median titers were 1,024 and 256, respectively, against the first and second virus. This would lend support to the seroswitch approach if antibodies were the crucial determinant of efficacy. However, as detailed in our article (2), this did not convert into a survival advantage suggesting that antiviral immunity is not automatically good or bad for efficacy.

The most intriguing question set forth by Prof. Harrington relates to our proposal that reduction of antitumor T cells in blood might be indicative of their trafficking to the tumor. Although this claim may seem somewhat provocative, there are some mouse and human data in support of this hypothesis, as discussed in the Results section of our article (2). A recent review on T-cell trafficking is also referenced below (6). Moreover, we are now in the process of analyzing biopsies from patients treated with oncolytic adenoviruses, which should clarify this important question.

In summary, it is clear that ATAP is not an alternative for trials, and certainly from the perspective of a biotechnology company aiming to develop their product toward corporate acquisition or market approval, trials may be a preferred option. Accordingly, the great majority of clinical trials in the oncolytic virus space is sponsored by companies. Now, after 15 years of painstakingly slow progress (except in China), randomized results from oncolytic virus trials are finally becoming available, as summarized by Prof.
Harrington. Perhaps the biggest news thus far was the press release from Amgen Inc. on March 19, 2013, where they indicated that they had reached the primary endpoint in their randomized phase III global melanoma trial featuring a granulocyte macrophage colony-stimulating factor (GM-CSF)–armed oncolytic herpes virus. The armed oncolytic virus improved the durable response rate significantly in comparison to GM-CSF alone. Therefore, there is no doubt that oncolytic viruses are moving forward in clinical trials. However, not all patients have access to such trials and thus there might also be a role for personalized therapy programs in the future. It will be interesting to see if it will be possible to marry the currently demanding production requirements with the condition of small-scale “nonindustrial” personalized treatment. The experience in Finland was that the per-patient cost of virus production became prohibitive. Finally, regulators assume that there will be a sponsor able to pay for virus production and testing. However, with the caveats associated with individualized patient-by-patient treatment, it will remain to be seen if sponsors think the experience gained justifies the cost, as clinical trials will still have to be done to move the product forward for ultimate drug approval.

**Disclosure of Potential Conflicts of Interest**

A. Hemminki is employed (other than primary affiliation; e.g., consulting) as a consultant and has ownership interest (including patents) in Oncos Therapeutics Ltd. No potential conflicts of interest were disclosed by the other authors.

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**References**


![Table 1. Neutralizing antibodies (NAb) in patients treated with 3 injections of oncolytic adenoviruses with different capsids (“seroswitch”, top part) or 3 injections of CGTG-102 only (bottom half)](https://example.com/table1.png)
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