*See pages 1649 and 1821*

## Treatment of Chemotherapy-Refractory Cancer in the Advanced Therapy Access Program

**To the editor:**

I thank Dr. Cripe for discussing some of the pros and cons of our Advanced Therapy Access Program (ATAP) in this issue's Editorial.[1] When I returned to Finland from the United States in 2002, I assumed that gene therapies could be given only in the context of clinical trials. In 2005, I learned from a department head at the Finnish Medicines Agency (FIMEA) that in Finland it is legal to treat a patient with any form of therapy if the physician has medical, scientific, or experience-based information to support the treatment choice and if the patient agrees, as also outlined in the World Medical Association Declaration of Helsinki. On a European level, the Advanced Therapies Regulation (EC/1394/2007) sought to determine rules for patient-by-patient use of gene therapy and cell products—the so-called hospital exemption. The goal was to apply regulation in an area where it had been lacking previously and to encourage scientific and medical progress by formalizing "phase 0"-type use.

In my opinion, every patient who cannot be cured with routine therapies should be offered a formal, scientifically grounded experimental approach that was first tested in the laboratory, and all of the data should be published. Although thousands of patients have been treated with oncolytic virotherapy with good safety and some evidence of efficacy, the approach remains experimental. The ATAP was set up to offer oncolytic-virus treatments to patients lacking access to clinical trials. The goals of the ATAP were, first, to help the patient and, second, to enable us to learn about the technology as we used it. Because the viruses used were designed to work in most tumors, the patient population resembles a typical phase I population, and, whereas the heterogeneity certainly brings its problems, it can also be seen as a strength—if a finding emerges in such a population, it is perhaps more likely to be important and generalizable to real-life patients. Key features of the ATAP include rigorous preclinical testing of each virus before patient treatment. Each patient is monitored for safety, efficacy, and survival, and the data are also reported to the FIMEA. To ensure complete transparency, all data are reported in peer-reviewed journals.

This program led to various important observations. When we discovered that oncolysis alone was unlikely to cure patients with advanced tumors, we moved to armed viruses.[2,3] Safety was good with all constructs, suggesting that improving selectivity is less critical than improving efficacy. One of the more prominent observations was the tremendous inflammation in treated tumors, an aspect that was not apparent in immunodeficient animals. The next step was to try to direct this immune response against the tumor, and several immunostimulatory transgenes were employed in this regard.[3,4] Because expression of the adenovirus receptor CAR is a potential problem in cancer therapy, we employed several capsid-modified viruses.[5–8]

Low-dose cyclophosphamide was used to reduce regulatory T cells,[9] and a calcium channel blocker was used to increase virus replication.[10] A critical observation was that size-based response criteria do not capture the efficacy of potent immunotherapeutics. Instead, metabolic criteria (positron emission tomography–computed tomography) or immune-relevant criteria, applied over a prolonged period of time, seem more useful.

Overall, 10 different viruses were used in a total of 290 patients whose tumors were progressing after all routine therapies had been exhausted. Each of the 821 treatments was individually designed, typically employing intratumoral injection with ultrasound or computed tomography guidance. Each treatment was designed based on a rapid cycle of bench to bedside and back. By contrast, with iterative phase I trials, each cycle takes years at best. I believe the faster learning process was in the interest of patients, because they were able to receive a more advanced treatment, giving them a greater likelihood of benefit.

The ATAP was never meant as a replacement for trials. However, even with our patient experience, trials were a labor-intensive and expensive endeavor, and eventually Oncos Therapeutics had to focus its resources on trials, thus putting the ATAP on hold. Personally, I am not sure whether oncolytic viruses or other viral gene therapeutics are feasible for true patient-by-patient use under the current interpretation of EC/1394/2007. If full good manufacturing practice is required, and the number of treated patients must be small to retain the non-industrial aspect, the per-patient production costs become prohibitive.

With 4.5 years of experience from ATAP, I believe we are now more likely to plan successful trials, which is important from an ethical perspective because it minimizes patient exposure to ineffective regimens. However, most important, behind the numbers there are the patient stories, each one different. On my office wall, there is a drawing by a patient who had a very advanced progressing sarcoma but is still alive 3.5 years later. A young woman with liver metastatic melanoma was surprised when she received a follow-up call from us 3 years after her first treatment because she had not seen an oncologist for several years. One woman had a huge progressing tumor in her right lung and was organizing the guest list for her funeral. Nine months later, she was free of symptoms and used the same list to invite people to her birthday party.

Because I have seen it with my own eyes, I know that oncolytic viruses constitute a potent technology even in humans. However, this technology differs from any other treatment modality out there in that it is much more complex with several modes of action. Hence, there is still a great deal for us to learn in order to use it optimally, and unfortunately the available animal models are poorly predictive of human data. Therefore, our rate of learning will be determined solely by the speed of clinical translation. In my opinion, ATAP-type approaches are well

suited for accelerating this process to help us design successful trials that will bring the technology to routine clinical practice as soon as possible.

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