Molecular Therapy
Editorial

Cancer gene therapy bears fruit

As a first-year clinical fellow in 1992, my classmate and now well-known pediatric neuro-oncologist, Mark Kieran, convinced our program director to send the two of us to the First International Conference on Gene Therapy of Cancer held at the Hotel del Coronado in San Diego. I was already armed with a PhD in genetics, and the nascent field of gene therapy had piqued my interest. The conference was truly an eye-opener; I was absolutely stunned and thoroughly excited by the plethora of creative ideas being discussed to use genes as cancer treatment. Although delivery methods ranged from naked DNA to DNA-coated gold beads shot from a "gene gun," the most common method was replication-defective adenovirus vectors. Fast forward 30 years, and we finally have achieved the first such adenovirus-based gene therapy FDA approved for cancer.[1]

Nadofaragene firadenovec-vncg (Adstiladrin) is a non-replicating recombinant Ad5 vector engineered to express type I interferon-α2b for patients with Bacillus Calmette-Guérin immunotherapy-unresponsive non-muscle-invasive bladder cancer with carcinoma *in situ*.[2] Although we should recognize the approval as a true milestone, in many ways it represents the lowest-hanging fruit in the cancer gene therapy world. By definition, this cancer is localized and superficial within the bladder lining, enabling localized catheter-mediated injection to minimize systemic side effects. Patients undergo complete tumor excision prior to vector administration, so gene therapy is targeting microscopic residual disease, not bulky or metastatic disease. While the actual mechanism of efficacy is not completely understood, it appears that no actual targeting to the tumor is required; the vector presumably transduces normal bladder epithelial cells that secrete interferon in the microenvironment to inhibit growth of remaining cancer cells. Indeed, following virus injection virtually all patients have detectable levels of interferon in the urine. Protein expression largely remains within an organ cavity, likely maximizing local concentrations by minimizing loss into the systemic circulation. Because the inside of the bladder is a relatively immune-privileged site, repeated injections (done every 3 months) continue to be effective despite generation of systemic anti-adenovirus immunity. Furthermore, as spelled out in a 2018 FDA guidance document,[3] there was no need for a randomized trial or comparative treatment arms because the outcome of patients is dismal and alternatives are minimally effective; the agreed upon acceptable primary outcomes for the single-arm study were rates of complete responses and durability, not the traditionally required overall survival rates compared with a control group.

Importantly, the approval validates the use of virus-mediated gene delivery in human patients to achieve prolonged expression of a therapeutic protein. A gene therapy approach represents a distinct advantage because the effects of a single injection last weeks compared with instillation of purified interferon protein, which only lasts hours. Thus, not only were many patients able to avoid cystectomy, but they did so with only infrequent treatments and tolerable side effects.

Several questions regarding this treatment remain. For example, it is unknown whether native adenovirus genes and capsid proteins contribute to the inflammation and antitumor efficacy relative to the expressed transgene. If the effect is primarily due to interferon, alternative non-viral methods of gene transfer might also be efficacious. The study also opens up the possibility of adding in other transgenes that might have different mechanisms of action and possibly elicit even more impressive results. Finally, can instillation of localized gene therapy be effective for cancer that has invaded the muscle or beyond? To the extent that it might generate adaptive immunity against tumor-associated antigens, bladder instillation of gene therapy might elicit an abscopal effect, as was seen with T-VEC in melanoma.[4]

The biggest unknown, however, is whether we can use gene therapy to pick off higher-hanging fruit. Most advanced solid tumors remain deadly. Barriers to immunotherapy abound, including suppressive cells, cytokines and metabolites; compromised perfusion; and extracellular barriers. What will be required to reach that high fruit? Conditionally replicating (oncolytic) viruses might be better suited to amplify transgene expression in bulky tumors and promote antitumor inflammation. Following the norms of conventional cancer therapy, combination therapies will likely be needed, although gene therapy as a platform can incorporate multiple genes in the same vector to provide combinatorial effects. While the recent FDA approval of Adstiladrin represents another step up the ladder, hopefully it will not take another 30 years to reach the higher branches.

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