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Molecular Therapy

Oncolytic Viruses: Immune or Cytolytic Therapy?

In 1298, King Henry III granted Oxford University its Royal Charter, unwittingly setting wheels in motion that ultimately led to the hosting of the 8th International Conference on Oncolytic Virus Therapeutics at the Oxford University Examination Schools (April 2014). The meeting (organized by Len Seymour, Kerry Fisher, and Christina Woodward) was, in my opinion, far and away the best of this series of meetings since the 2001 inaugural event at the Mayo Clinic. Aside from the great food, venue, and camaraderie that we have come to expect from these events, there was clearly much excitement about the prospects for a US Food and Drug Administration–approved oncolytic virus (OV) product. Robert Coffin was the first-ever recipient of the Golden Virus Award, an honor to henceforth be bestowed on the scientist thought to have the biggest impact that year on the OV field. Rob was the unanimous choice, owing to his role in the development of T-Vec, a herpes simplex 1–based vector engineered for greater selectivity for tumor cells and more robust activation of the immune system. In a recently completed phase III study in melanoma, this Amgen product met its primary end point of durable response in patients with metastatic melanoma, and, although the trial was not powered for survival, T-Vec missed showing an overall survival benefit by the slimmest of margins. Amgen appears armed with a very compelling data package, and we anxiously wait to see when they will file for approval.

A variety of OVs are showing clinical activity in brain malignancies. Matthias Gromeier presented data from two glioblastoma (GBM) patients whose refractory tumors showed long-term complete responses following a single treatment with his oncolytic poliovirus–based PV-RIPO vector. Juan Fueyo presented similar clinical activity in GBM patients treated with a modified adenovirus (DNATrix's DNX-2401). Additional provocative clinical data from studies in GBM patients was presented by Doug Jolly of Tocagen, whose group used a replicating oncolytic retrovirus, and Tomoki Todo from Tokyo, who used an engineered herpes simplex virus. Not far behind on the developmental path, we saw impressive preclinical data in brain cancer models with two rhabdovirus products: a chimeric version of vesicular stomatitis virus (Alexander Muik) and Farmington virus (Dave Stojdl). For the sake of the victims of this dread disease, let's hope that the OV momentum in this indication continues and an approved product is on the way.

Are OVs really direct tumor killers or simply immune adjuvants? This remains an ongoing debate in the field—"purists" believe that it is the cytolytic activity of OVs that is the most important component of the platform whereas a growing number of researchers argue that long-term benefit of OV therapy depends on the generation of an antitumor immune response. In general, through expression of a variety of gene products, malignant cells cloak themselves in an immunosuppressive microenvironment, thus avoiding detection and destruction by cytolytic T cells. Under the stress of a virus infection, however, tumors express a number of proinflammatory molecules sending out signals that lead to localized recruitment and activation of immune cells. In addition, the lysis of cancer cells by OVs leads to the liberation of tumor antigens and expression of danger signals, effectively creating an "*in situ*" vaccine. Although the mechanism of OV activation of antitumor immunity has been primarily worked out in mouse models, there is increasing clinical evidence that this phenomenon occurs in patients as well. In the brain tumor and T-Vec studies described above, clinical responses were often delayed, suggesting an immune-mediated mechanism of action.

Antitumor immunity is often ineffective, owing to the phenomenon of "T-cell exhaustion" following chronic exposure to antigens, and is associated with the expression of inhibitory receptors. These inhibitory receptors normally serve as immune checkpoints designed to prevent uncontrolled immune reactions. The checkpoints can be blocked using monoclonal antibodies specific to the inhibitory receptors, thereby rescuing otherwise exhausted antitumor T cells. Several groups have tested the idea that OV therapeutic activity can be enhanced through combination with such immune-checkpoint inhibitors, with perhaps the most compelling data at the meeting presented by Darren Shafren with the coxsackievirus product CV-21.

On the other side of the ledger, Steve Russell presented exciting data from a myeloma patient with widespread disease treated with an oncolytic measles virus expressing the gene encoding the sodium iodide symporter. Following a single intravenous infusion, this patient experienced a complete pathological response and remained free of disease for 9 months. Using the sodium iodide symporter gene as an imaging tool, Steve and his colleagues revealed clear OV activity in distant lesions. This study, and others using the Jennerex virus Pexa-Vec (Caroline Breitbach) and the PsiOxus virus ColoAd1 (Kerry Fisher) in colon cancer patients, demonstrated that widespread intravenous delivery of OVs is possible in cancer patients. Despite the success to date of locoregional approaches for OV therapy (T-Vec and GBM studies), it remains an open question as to whether intravenous, intratumor, or, perhaps, a combination of the two is the best mode of OV delivery.

Where will the OV field be in five years? There is little doubt that OVs in general have finally begun to pique the interest of the pharmaceutical and biotechnology industries. The excitement that immune-checkpoint inhibitor antibodies have attracted in the clinic is certainly justified, but many believe these reagents will really excel when thoughtfully partnered with other immune-modulating agents. The ability of OVs to reverse the immunosuppressive tumor microenvironment and generate or amplify T cell–mediated antitumor immune responses makes them ideal candidates to complement immune-checkpoint inhibitor therapeutics such as anti-PDL-1 and anti-CTLA4. Given the heterogeneity of cancers, it seems unlikely that either platform (immune-checkpoint inhibitor or OV) alone will suffice to effect cures in the majority of patients, but their combination just might.

Next June in Boston, Nino Chiocca and Sam Rabkin will host the 9th International Conference on Oncolytic Virus Therapeutics, and I expect we will see more preclinical and clinical data supporting the power of immune-checkpoint inhibitor–OV combinations and perhaps further integration of OVs into the mainstream pharmaceutical industry.

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