Editorial
Engineering Viruses to Fight Cancer

With EMA approval in December 2015, and US FDA approval in October 2015 of an oncolytic herpesvirus for the treatment of non-resectable melanoma, we now have a novel class of anticancer agents to add to our ever-promising arsenal of cancer (immuno-) therapeutics.

Talimogene laherparapvec (T-VEC) therapy involves direct, intratumoral injection of a herpes simplex type 1 (HSV-1) virus which has been genetically altered to decrease pathogenicity, and to stimulate the host’s own immune response by both expressing the immune-stimulatory cytokine GM-CSF as well as increasing the presentation of tumor antigens by the infected cell. In this sense, the approach is “two-pronged” in that the virus is not only designed to infect and destroy cancer cells and leave healthy ones alone, but—in doing so—the virus infection and subsequent breakdown of the tumor cells help to stimulate the immune system to recognize and kill these infected cells, as well as other cells expressing the same patient-specific tumor antigens.

A Phase 3 randomized clinical trial (OPTiM) published earlier in 2015 looked at T-VEC treatment in stage IIIB-IV melanoma patients. Results indicated that T-VEC was relatively well tolerated, and significantly improved the overall durable response rate (DRR) compared to GM-CSF treatment alone (16.3% versus 2.1%, respectively), meeting the primary endpoint of the study. DRR to T-VEC was even more pronounced in patients with less advanced melanoma (33%, compared to 0% in the GM-CSF treatment group). Although overall survival was not significantly extended (4.4 months, \( P = .051 \)), the results are widely heralded as a major success as they provide proof of principle that oncolytic viruses are a viable class of anticancer treatments ready for application in the clinic.

Indeed, several other clinical trials are underway to examine whether other cancers may be similarly treated with either modified HSV or other engineered viruses. Researchers at Duke University, for example, have shown encouraging results in a Phase 1 study treating recurrent glioblastoma patients with modified poliovirus, also by injecting the therapeutic virus directly into the patient’s tumor. This particular poliovirus strain was altered in the laboratory (20 years ago) by replacing part of its RNA (the internal ribosomal entry site, or IRES) with the equivalent IRES sequence from human rhinovirus. The resultant chimeric virus is still able to bind to and enter glioblastoma cells, which happen to express high amounts of poliovirus receptor — but the genetic alteration reduces its neuropathogenic potential. Although results from the trial using this virus are still quite preliminary, they are indeed striking—with a number of patients apparently experiencing a complete disappearance of their tumors. Given that this type of cancer often has a very poor prognosis, this is an encouraging potential new option for the field.

Another promising example of oncolytic viruses as a treatment option is the use of an altered vaccinia virus, JX-594 (pexastimogene devacirepvec [Pexa-Vec]), for the treatment of hepatocellular carcinoma (HCC). Following positive Phase 2 results where median survival was significantly extended, a global Phase 3 randomized clinical trial has just begun recruiting (PHOCUS) which uses JX-594 in combination with the kinase inhibitor sorafenib for the treatment of advanced HCC patients. Control patients will receive sorafenib alone, which is already in clinical use as the only approved HCC pharmacological therapeutic. The backbone of JX-594 is a strain that has been used safely for many years for smallpox vaccination. In addition, the virus has a genetic deletion which removes the viral thymidine kinase (TK) gene. This alteration renders the virus dependent upon cellular TK, which is expressed at persistently high levels in cancer cells—therefore providing a replication advantage in cancer cells over healthy ones. Like T-VEC, JX-594 also expresses the immune-stimulatory GM-CSF protein to help boost host anti-tumor responses.

A search performed in January 2016 for clinical trials (www.clinicaltrials.gov) employing the use of oncolytic viruses as a therapeutic returned dozens of trials, at all stages of investigation. These trials employ the use of multiple viral vectors and target a wide range of cancers including ovarian cancer, metastatic colorectal cancer, advanced pancreatic adenocarcinoma and a variety of other solid tumors. Given the recent approval of T-VEC as the first oncolytic virus approved for the clinic, this list is expected to increase as we think of new ways to use this exciting new tool to combat cancer.

But what’s next for the field?

A better mechanistic understanding of how these therapies are working (when they work well), and what fails when they don’t work, will help researchers design next-generation oncolytic virus therapies. For example, what factors render a cancer cell more or less susceptible to infection and lysis by the virus? Which viral vectors are best suited for each particular cancer, and for specific modes of delivery? What host immune pathways are necessary to mount an effective response to the infected/lysed tumor cells, and how can this be increased at both the injected tumor site as well as systemically at peripheral tumors? What immunosuppressive pathways are working against effective oncolysis?

Related to this last point, a clinical trial is already underway looking at T-VEC in combination with the CTLA-4 inhibitor ipilimumab in late-stage melanoma patients. Given the huge promise of checkpoint inhibitors and these early encouraging results with first-generation oncolytic virus therapies, we eagerly await the next chapter of this exciting new cancer treatment modality.

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