Can Viruses Be Used to Treat Cancer?

An oncolytic virus that kills cancer cells and triggers immune responses against tumors shows promise for children with brain cancer.

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An experimental immunotherapy that uses a genetically engineered herpes virus to target tumors has shown promising results for children and adolescents with glioma brain cancer, according to a report at the American Association for Cancer Research (AACR) virtual annual meeting. Researchers also presented early data on other oncolytic viruses being developed to treat various types of cancer.

It's well known that some viruses, including human papillomavirus and hepatitis B and C viruses, can cause cancer. But others are cancer killers. Oncolytic viruses both destroy cancer cells directly and promote immune responses against tumors—an approach dubbed immunovirotherapy. These viruses enter tumor cells and replicate, rupturing the cells and releasing viral progeny that attack other tumor cells and cancer proteins that trigger an inflammatory response. One engineered oncolytic herpes virus, Imlygic (talimogene laherparepvec), is currently approved as a treatment for advanced melanoma.

Treating Brain Cancer With Viruses

Gregory Friedman, MD, of the University of Alabama at Birmingham, presented results from a study of G207, an oncolytic virus being developed by the biotechnology company Treovir, as a treatment for pediatric patients with recurrent or progressive glioma. The findings were also published in The New England Journal of Medicine.

Gliomas are so-called cold tumors that don't provoke a strong natural immune response and generally respond poorly to immunotherapy such as checkpoint inhibitors. The usual approach for high-grade glioma—including its most advanced stage, glioblastoma—involves surgery, radiation therapy and chemotherapy. But the treatment is difficult to tolerate, recurrence is common and survival is typically short.

"Unfortunately, outcomes are very poor for children with progressive gliomas, and we have not seen a significant improvement in outcomes for this dreadful disease in the last 30 years," Friedman noted in an AACR press release.

G207 is an engineered form of herpes simplex virus type 1 (HSV-1)—the virus that causes cold sores—which naturally infects cells in the central nervous system. The virus has been modified so

that it only infects cancer cells while leaving normal cells unharmed.

The Phase I study (NCT02457845) enrolled 12 patients, ages 7 to 18 years old, with high-grade glioma that had relapsed or progressed despite prior treatment. Ten had glioblastoma, 10 had large tumors and three had multiple tumors. A majority had received at two or more lines of prior therapy.

The participants received a single infusion of G207 administered into the brain through a catheter. Half also received a small dose of radiation delivered within 24 hours after the infusion, which was intended to promote replication and release of the virus.

The treatment was well tolerated, with no drug-related serious adverse events; most side effects were mild. No viral shedding was observed in the blood or saliva, meaning the experimental virus won't be transmitted to others.

"This is the first study utilizing delivery of a viral immunotherapy directly into brain tumors in children, and the results indicate that G207 can be delivered safely into tumors located in all areas of the cerebrum in children," Friedman said in a Treovir press release. "The key findings thus far are that the approach is safe and well tolerated, and the preliminary evidence of efficacy is very promising."

Eleven of the 12 children responded to the treatment, experiencing tumor shrinkage or dissolution (what Friedman described as a "Swiss cheese response") or clinical improvement. The median overall survival time was 12.2 months—more than twice the expected duration for untreated pediatric patients with recurrent high-grade glioma. Four study participants were still alive 18 or more months after treatment, surpassing the expected survival time for children with newly diagnosed high-grade glioma.

What's more, the children showed strong local immune responses, with an increase in the number of tumor-infiltrating lymphocytes (TILs), or cancer-fighting T cells. Both CD4 helper T cells and CD8 killer T cells increased within two to nine months after receiving G207, and immune cells were seen even beyond the infusion site. In effect, the treatment turned cold tumors hot.

"These results indicate that this treatment can transform immunologically 'cold' pediatric high-grade gliomas with very few immune cells into 'hot' tumors with an abundance of immune cells, which is a critical step in the development of an effective immunotherapy for children with brain tumors," Friedman said.

However, survival was less impressive in children who had pre-existing antibodies against HSV-1. This might help explain why G207 did not work as well in previous studies of adults with brain cancer: By the time they're adults, most people have already been exposed to HSV-1.

Treovir indicated that it expects to launch a follow-up Phase II trial of G207 for children with

recurrent high-grade glioma (NCT04482933) later this year. The company also plans to study G207 in patients with newly diagnosed glioma. The treatment is also under evaluation for other types of pediatric brain cancer, including medulloblastoma, the most common type of malignant tumor in children.

Other Oncolytic Viruses

G207 is far from the only oncolytic virus being studied for cancer treatment.

Preclinical studies presented at AACR showed that two other versions of a modified herpes virus being developed by Replimune, dubbed RP1 and RP2, demonstrated potent antitumor activity and triggered a robust systemic immune response, according to the company.

When administered with the checkpoint inhibitor Opdivo (nivolumab), the viruses increased PD-L1 expression in different types of cancer and promoted infiltration of CD8 T cells into tumors. Researchers also observed increased expression of genes associated with innate and adaptive immune activation. In a mouse study, tumors injected with RP1 or RP2 showed large areas of necrosis, or cell death, and even uninjected tumors shrank.

“RP1 and RP2 represent attractive potential treatment modalities with the ability to self-amplify, kill through multiple mechanisms and promote antitumor immune responses,” Kevin Harrington, PhD, of the Royal Marsden NHS Foundation Trust in London, said in a Replimune press release. “These benefits are then further enhanced by treatment with anti-PD1 [checkpoint inhibitor therapy] creating the potential for an attractive treatment option for patients with difficult to treat tumor types who are currently underserved.”

Finally, other preclinical data presented at the meeting showed that an engineered myxoma (rabbit pox) virus being developed by OncoMyx was active against multiple human cancer cell lines in laboratory studies, and it slowed tumor growth in mice implanted with human non-small-cell lung cancer, breast cancer, bone cancer and melanoma.

The experimental virus, which doesn’t cause disease in humans, is armed with genes encoding the cytokine interleukin 12 and a protein known as decorin. It is designed to both promote immune activity against tumors and overcome cancer’s ability to suppress immune responses. The virus upregulates genes associated with immune response and increases the number of cancer-fighting immune cells entering tumors—and it works even better when combined with checkpoint inhibitors.

Researchers have studied both direct injection of the virus into tumors and administration via IV infusion—a potentially more promising approach for reaching inaccessible tumors. IV administration could potentially trigger an excessive immune response that harms healthy organs and tissues, but computer modeling suggests that cytokine levels should remain within a known safety margin, company scientists reported.

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