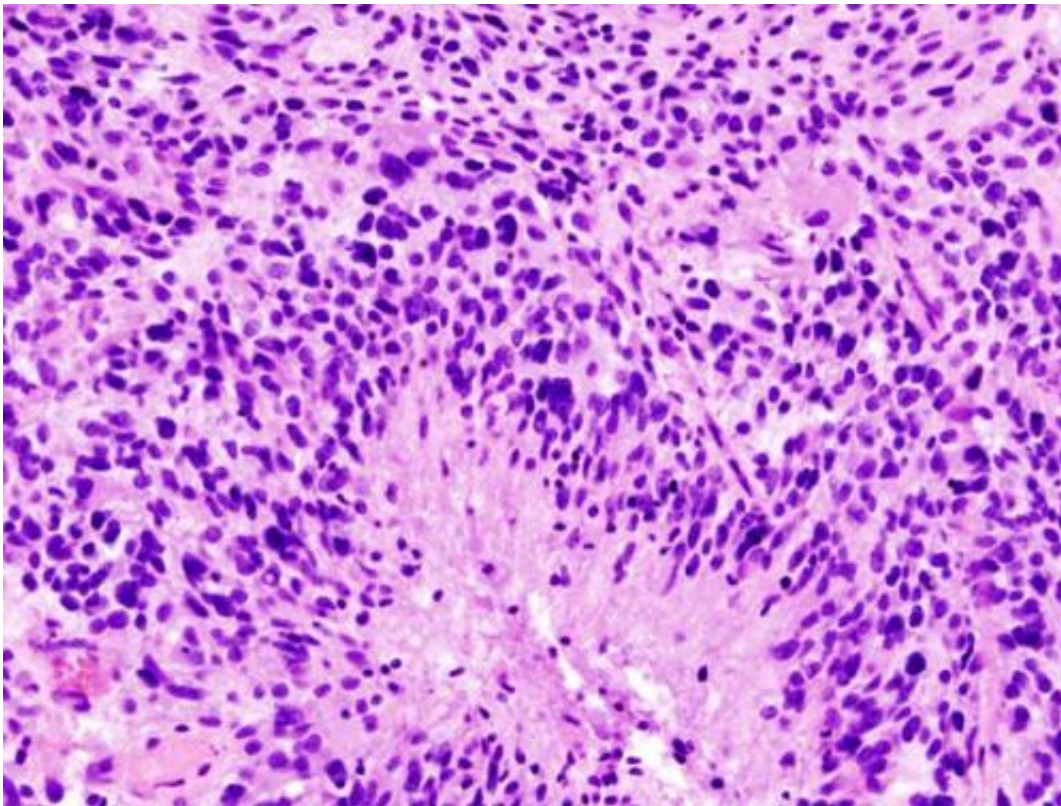


Researchers test novel gene therapy for glioblastoma

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Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

A novel gene therapy clinical trial at University Hospitals Seidman Cancer Center and the Case Comprehensive Cancer Center is showing promising results, garnering funding with a prestigious U01 Grant from the National Cancer Institute. The trial focuses on turning patients with a poor prognosis into those with a good prognosis.

This trial involves glioblastoma multiforme (GBM), the deadliest form of brain cancer and among the most difficult cancers to treat. The mean survival from the time of diagnosis is only about one year. In the trial's Phase 1, which focuses on assessing safety rather than clinical benefit, median survival of GBM [patients](#) was 3.5-fold the expected survival based on published modeling studies with actual data from patients with similar situations in randomized [clinical trials](#).

A \$2.7 million grant to further the gene therapy study was awarded to Andrew E. Sloan, MD, Director of the Brain Tumor & Neuro-Oncology Center and the Center of Excellence for Translational Neuro-Oncology (CETNO) at UH Cleveland Medical Center and UH Seidman Cancer Center, and Stanton Gerson, MD, Director of the Case Comprehensive Cancer Center. Results of the Phase 1 clinical trial will be shared on June 2 at the American Society of Clinical Oncology's annual meeting in Chicago.

Their trial centers on the efficacy of the chemotherapeutic agents O-benzylguanine (BG) and temozolomide (TMZ) and repair enzyme MGMT, known to be an important prognostic indicator in GBM.

Since 2005, physicians have found GBM patients fall into one of two categories. Patients whose MGMT promotor is methylated and thus don't produce much of the repair enzyme MGMT comprise the "good prognosis" group. For these patients, chemotherapy and radiation work well, and almost 50 percent of them live for two years. About 55 percent of patients, however, are unmethylated and make considerable MGMT that protects the tumor from chemotherapy. This "[poor prognosis](#)" group has a median survival of only 13.8 months.

"We began to wonder if we could convert patients from 'poor prognosis' to 'good prognosis' by inhibiting MGMT with BG," Dr. Sloan said. "BG has two different effects: 1) It disables the tumor from repairing the

damage induced by chemotherapy, and 2) By poisoning the bone marrow, the BG makes the body more sensitive to the side effects of radiation therapy.

"What if we could separate those two populations—the tumor and the bone marrow—and treat them as different compartments in the body?"

This, Dr. Sloan said, led to the idea of using gene therapy to alter MGMT.

Dr. Gerson developed a mutant gene called P140K, which does not bind to BG but repairs DNA damage caused by temozolomide. He and Dr. Sloan then took hematopoietic stem cells from patients' blood through leukopheresis, genetically engineered them to produce P140K to make them resistant to chemotherapy, and then re-infused them into the patient to protect the bone marrow. This study is coordinated under a cooperative agreement with investigators at NCI with some patients treated there as well, Dr. Gerson said.

The gene therapy was notably done with a new safety-modified lentiviral vector similar to those used for CAR T cell therapy. Results to date have been promising.

"Stan Gerson has been working on MGMT for 30 years and is the world expert," Dr. Sloan says. "It turns out that GBM is the one cancer where it really makes a difference!"

The trial has progressed with very few side effects among the patients. All eligible patients tolerated at least one cycle of progressively increased dosage of chemotherapy, with five cycles of dose escalation of BG and TMZ as the median. Median survival was 3.5 times longer than expected, and the MGMT mutant was 3 to 26 times higher in peripheral blood than in untreated patients.

"This regimen was tolerable, safe, and enabled dose escalation of chemotherapy with impressive improvement in survival compared to a large set of case-matched studies," Dr. Sloan said.

Drs. Sloan and Gerson also are considering the best sequence of surgery, radiation, chemotherapy and the reinfusion of genetically engineered stem cells. The Phase I trial tested three possible sequences.

Remarkably, three of five patients in one of the three cohorts not only survived three years, but had no disease recurrence after that time period. Five of the 10 patients in the trial have survived more than four times longer than expected.

These highly encouraging results convinced the NCI to fund the U01 thus driving the protocol into a multi-center Phase 2 clinical trial. In this next phase, which will open before the end of the year, Dr. Sloan said the team plans to examine interactions with the immune system and explore as well as how and why the tumor returns in some patients.

Provided by University Hospitals Cleveland Medical Center

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