Gene-modified stem cell transplant protects patients from toxic side effects of chemotherapy

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For the first time, scientists at Fred Hutchinson Cancer Research Center have transplanted brain cancer patients' own gene-modified blood stem cells in order to protect their bone marrow against the toxic side effects of chemotherapy. Initial results of the ongoing, small clinical trial of three patients with glioblastoma showed that two patients survived longer than predicted if they had not been given the transplants, and a third patient remains alive with no disease progression almost three years after treatment.

"We found that patients were able to tolerate the chemotherapy better and without negative side effects after transplantation of the gene-modified stem cells than patients in previous studies who received the same type of chemotherapy without a transplant of gene-modified stem cells," said Hans-Peter Kiem, M.D., senior and corresponding author of the study published in the May 9 issue of *Science Translational Medicine*.

Kiem, a member of the Clinical Research Division at the Hutchinson Center, said that a major barrier to effective use of chemotherapy to treat cancers like glioblastoma has been the toxicity of chemotherapy drugs to other organs, primarily bone marrow. This results in decreased blood cell counts, increased susceptibility to infections and other side effects. Discontinuing or delaying treatment or reducing the chemotherapy dose is generally required, but that often results in less effective treatment.

In the current study, Kiem and colleagues focused on patients with glioblastoma, an invariably fatal cancer. Many of these patients have a gene called MGMT (O6-methylguanine-DNA-methyltransferase) that is turned on because the promoter for this gene is unmethylated. MGMT is a DNA repair enzyme that counteracts the toxic effect of some chemotherapy agents like temozolomide. Patients with such an unmethylated promoter status have a particularly poor prognosis.

A drug called benzylguanine can block the MGMT gene and make tumor cells sensitive to chemotherapy again, but when given with chemotherapy, the toxic effects of this combination are too much for bone marrow cells, which results in marrow suppression.

By giving bone marrow stem cells P140K, which is a modified version of MGMT, those cells are protected from the toxic effects of benzylguanine and chemotherapy, while the tumor cells are still sensitive to chemotherapy. "P140K can repair the damage caused by chemotherapy and is impervious to the effects of benzylguanine," Kiem said.

"This therapy is analogous to firing at both tumor cells and bone marrow cells, but giving the bone marrow cells protective shields while the tumor cells are unshielded," said Jennifer Adair, Ph.D., who shares first authorship of the study with Brian Beard, Ph.D., both members of Kiem's lab.

The three patients in this study survived an average of 22 months after receiving transplants of their own circulating blood stem cells. One, an Alaskan man, remains alive 34 months after treatment. Median survival for patients with this type of high-risk glioblastoma without a transplant is just over a year.

"Glioblastoma remains one of the most devastating cancers with a

median survival of only 12 to 15 months for patients with unmethylated MGMT," said Maciej Mrugala, M.D., the lead neuro oncologist for this study.

As many as 50 percent to 60 percent of glioblastoma patients harbor such chemotherapy-resistant tumors, which makes gene-modified stem cell transplant therapy applicable to a large number of these patients. In addition, there are also other brain tumors such as neuroblastoma or other solid tumors with MGMT-mediated chemo resistance that might benefit from this approach.

The researchers also found that chemotherapy increased the number of gene-modified blood and bone marrow cells in these patients. Kiem said this finding will have implications for other stem cell gene therapy applications where defective bone marrow stem cells can be corrected by gene therapy but their numbers need to be increased to produce a therapeutic benefit, or for patients with HIV/AIDS to increase the number of HIV-resistant stem and T cells.

More information: *Science Translational Medicine* paper is called "Extended Survival of Glioblastoma Patients After Chemoprotective HSC Gene Therapy."

The clinical trial is open and is recruiting more patients. For more information go to: clinicaltrials.gov/ct2/show/NCT00669669

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