Modified Stem Cells Prevent Chemotherapy's Toxic Side Effects

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JR Schoenborn

Many chemotherapeutic agents impair DNA replication or other cell division processes, thus killing rapidly dividing tumor cells. However, chemotherapy also harms host cells that divide frequently, including cells of the bone marrow, hair follicles and those that line the intestine. These toxic side effects have long been a challenge for effective cancer treatment. In particular, bone marrow toxicities can lead to a severe loss of platelets and red and white blood cells, which increases the patient's susceptibility to infection and their risk of bleeding. As a result, a delay or discontinuation of treatment may be required to allow patients to recover, but is associated with lower treatment efficacy.

To make patients' bone marrow cells more resistant to treatment-associated toxicities, Drs. Jennifer Adair and Hans-Peter Kiem and colleagues in the Clinical Research Division have isolated, modified, and reintroduced brain cancer patients' hematopoietic stem cells (HSC). In addition to being able to handle chemotherapy better, patients have had improved survival.

The crucial element to this research was the identification and modification of a key DNA repair enzyme that is responsible for mending DNA damage in cells that have been exposed to alkylating agents used for chemotherapy. This enzyme, MGMT (methylguanine methyltransferase), is generally not expressed at high levels in healthy tissue. In contrast, MGMT is often up-regulated in grade IV brain tumors as a result of DNA demethylation. This allows brain tumors to repair chemotherapy-induced DNA damage, leading to chemo-resistance. In contrast, healthy bone marrow cells cannot effectively repair the DNA damage, and suffer from toxic side effects of chemotherapy. To overcome the sensitivity of the bone marrow to chemotherapy, the authors isolated and modified HSC from three patients with advanced, chemo-resistant glioblastoma. Hematopoetic stem cells were transduced with an altered MGMT (P140K) enzyme that is resistant to MGMT inhibitors but maintains DNA repair activities. Following reinfusion of the cells, the patients were given increasing doses of chemotherapy designed to induce DNA damage and inhibit MGMT-mediated DNA repair in the tumor.

Following gene therapy, patients tolerated chemotherapy well and have had improved survival. Generally, glioblastoma is detected and diagnosed when it's at an advanced stage with no effective treatments. The median survival time for similar glioblastoma patients with standard treatment is 12-15 months. However, the three patients in this study have had an average survival time of 22 months, with one patient alive and progression-free more than two years following diagnosis. MGMT-modified granulocytes and lymphocytes, major constituents of the immune system, were detected in patients' peripheral blood for over a year following gene therapy. Furthermore, MGMT-modified cells were derived from a diverse array of different bone marrow stem cells, as shown by analysis of MGMT vector integration sites. Thus, gene therapy led to a breadth and durability of bone marrow cells that are protected from chemotherapy-induced toxicities.

These results indicate the utility of genetically-modified HSC for chemoprotection in cancers that are treated using alkylating agents. Further refinements of this technology are likely to improve the treatment of a variety of cancers and other diseases.

Adair JE, Beard BC, Trobridge GD, Neff T, Rockhill JK, Silbergeld DL, Mrugala MM, Kiem H. 2012. Extended survival of glioblastoma patients after chemoprotective HSC gene therapy. *Science Translational Medicine* 4(133):133ra57.

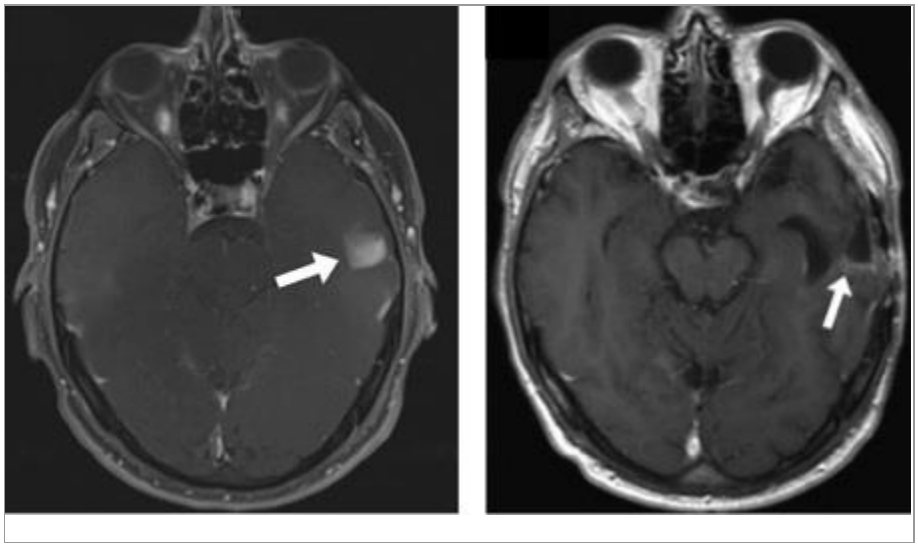

Image courtesy of authors

Stable glioblastoma in a patient one year following diagnosis and treatment. Left panel: grade iv glioblastoma marked by arrow. Right panel: tumor region (arrow) following surgery and four rounds of chemoprotective HSC gene therapy and chemotherapy shows stable disease.