Cancer-fighting cells' potency in melanoma patients extended by new technique

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Like brainy bookworms unprepared for the rough and tumble of post-graduation life, white blood cells trained by scientists to attack tumors tend to fade away quickly when injected into cancer patients. Dana-Farber Cancer Institute scientists, however, have developed a technique that can cause such cells to survive in patients' bloodstreams for well over a year, in some cases, without the need of other, highly toxic treatments, a new study shows.

In a paper published in the Apr. 27 issue of *Science Translational Medicine*, the researchers report the results of a small, Phase I study in which the technique -- a form of "adoptive immunotherapy" -- was tested in nine patients with advanced melanoma. Ten weeks after starting the therapy, seven of the nine patients had more of the specially trained, tumor-hunting cells than they had started with. Three of the patients had stable disease -- neither advancing nor retreating -- and one had shrinkage of a tumor that had spread to the lung. Another patient experienced a complete remission, with no tumors visible on CT or PET scans. Today, 25 months after receiving the one-time therapy, he has no evidence of cancer.

The results represent the longest that the injected cells -- known as anti-tumor T cells -- have ever endured in cancer patients without the use of supplemental treatments -- treatments that, while effective, often have harsh side effects. "The study demonstrates it is possible to maintain high levels of anti-tumor T cells in patients over a long period of time while avoiding the complications of conventional approaches," says the

study's lead author, Marcus Butler, MD, of Dana-Farber's Early Drug Development Center. "Our technique opens the way to therapies that produce less-toxic, long-lasting immune system attacks on cancer cells."

The technique's promise was further illustrated when researchers combined it with another treatment. Five patients whose disease had progressed after T cell infusions were treated with ipilimumab, a drug that boosts the cells' anti-tumor response. Three of the patients had long-term shrinkage of their tumors, and two others had their disease stabilize. Patients who received the drug after the completing clinical trial had sizable increases in the number of anti-tumor T cells in their blood.

Melanoma skin cancers were diagnosed in more than 68,000 Americans in 2010, according to the American Cancer Society, and the numbers have been rising for more than 30 years. If detected and removed at an early stage, melanomas can usually be cured, but once the disease has spread to distant sites, the median survival time for patients is less than a year. Scientists are developing an array of novel treatment approaches to improve those odds.

Adoptive immunotherapy involves collecting T cells -- natural infection- and cancer-fighters of the immune system -- from a patient and exposing them to protein "antigens" found only on tumor cells. The T cells learn to recognize the antigens and to attack tumor cells that carry them. Technicians treat these "educated" T cells with a growth stimulator to increase their number and then inject them back into the patient, where they fan out to obliterate tumor cells.

Under normal conditions, the reinjected T cells die off in a matter of days. Doctors can increase their staying power by depleting patients' blood of certain regulatory T cells that dampen the anti-tumor T cells' response to cancer or using Interleukin 2, which spurs the growth of T

cells. Both techniques can cause a host of health problems, including nausea, fever, muscle weakness, a drop in certain kinds of white blood cells, as well as other, more severe ones.

The technique developed at Dana-Farber aims to reduce those problems while giving anti-tumor T cells the stamina to persevere in the body. It involves an artificial version of cells known as antigen-presenting cells. Such cells act like tiny "FBI Most Wanted" posters: by displaying tumor cell antigens, they inform the immune system that cancer is present and needs to be eliminated. Dana-Farber scientists engineered antigen-presenting cells to produce a key molecule, known as CD83, which ensures that T cells persist for a long period of time. They also used Interleukin 15 to educate the T cells to be survivors. These educated T cells, known as memory cells, use their "knowledge" of tumor antigens to prepare them to launch a swift, powerful attack on tumor cells.

Follow-up exams of study participants showed that blood levels of educated anti-tumor T cells remained elevated many months after treatment and congregated inside the melanoma tumors. By observing how the cells function, investigators confirmed that they were indeed memory cells -- and therefore the descendants of the ones that had been educated in the lab -- not untrained T cells that had yet to encounter cancer cell antigens.

The researchers found that patients with the highest post-treatment levels of anti-tumor T cells did not necessarily fare better than those with lower levels. This wasn't surprising, they say, because many tumors have developed an ability to blunt a T cell attack.

As a phase I trial, the study was primarily concerned with the safety of the technique and with its ability to produce long-lasting anti-tumor T cells in patients. The striking results in the patient who is cancer-free two years after completing therapy were unexpected, the authors say, but

offer a glimpse of the technique's effectiveness when refined and combined with other agents.

"Our next step will be to study this technique in conjunction with other therapies that can boost the numbers and effectiveness of these memory T cells," says the study's senior author, Naoto Hirano, MD, PhD, of Dana-Farber and the Ontario Cancer Institute in Toronto. "We will be beginning a series of clinical trials to learn which combinations work best in which patients."

Provided by Dana-Farber Cancer Institute