Study finds promise in combined transplant/vaccine therapy for high-risk leukemia

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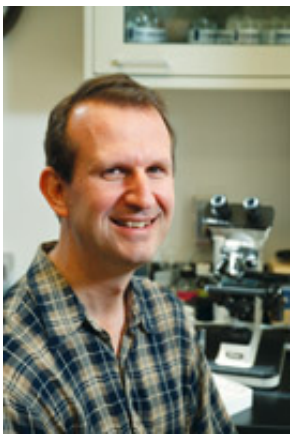

The key to the technique's success was the timing of the vaccine, explained the study's co-senior author, Harvard Medical School associate professor Glenn Dranoff, of DFCI. Photograph by Steve Gilbert

(PhysOrg.com) -- Two of the most powerful approaches to cancer treatment -- a stem cell transplant and an immune system-stimulating vaccine -- appear to reinforce each other in patients with an aggressive, hard-to-control form of leukemia, Dana-Farber Cancer Institute scientists have found.

In a study to be published in the online early edition of the Proceedings of the National Academy of Sciences the week of Aug. 24, the

researchers report that patients with high-risk acute myeloid leukemia (AML) or advanced myelodysplasia (a blood disorder) who received a cancer vaccine shortly after a stem cell transplant not only had few complications but also mounted a strong immune system attack on the disease. Particularly encouraging was the fact that rates of graft-versus-host disease (GVHD), a potentially severe aftereffect of immune system-based therapies, were no higher than with stem cell transplants alone.

The key to the technique's success was the timing of the vaccine, explained the study's co-senior author, Glenn Dranoff, MD, of Dana-Farber. "In previous studies that have combined stem cell transplantation with a cancer vaccine, the vaccine wasn't given until a significant amount of time after the transplant," said Dranoff. "In research with animal models, we found the approach works best if the vaccine follows the transplant by just a few weeks."

The study involved 28 patients with advanced myelodysplasia or high-risk AML ("high-risk" meaning their disease did not respond to standard chemotherapy treatment). Twenty-four underwent a transplant of hematopoietic (blood-making) stem cells: after receiving chemotherapy to reduce the number of diseased blood-forming cells in their bone marrow, they received an infusion of healthy stem cells from a matched donor. The transplanted cells settled in the bone marrow, where they began to regenerate patients' blood supply, including white blood cells and other agents that constitute the immune system.

Between 30 and 45 days after transplant, 15 of the patients began receiving a cancer vaccine. The vaccine was made by surgically removing cancerous or myelodysplasic tissue from patients and genetically altering the diseased cells so they would produce a protein called GM-CSF. When these modified cells were injected into patients as a vaccine, the cells began pumping out GM-CSF. Just as a matador's cape provokes the bull to attack, GM-CSF spurred the immune system to

attack cancer cells throughout the body.

Ten of the participating patients completed the full course of six vaccinations (the others had to drop out of the trial because of rapidly advancing disease). All of the patients who received even a single vaccination had a better survival rate than people with these diseases customarily have. Of the 10 who received the entire vaccine course, nine are alive and in full remission up to four years after treatment.

Although the only way to determine whether the combined transplant/vaccine approach is superior to transplant alone is to compare them head-to-head in a clinical trial, the results of the current study are highly encouraging, said co-senior author Robert Soiffer, MD, of Dana-Farber. Historically, only about 20 percent of similar high-risk AML and myelodysplasia patients who receive a transplant survive for at least two years.

Researchers believe the new approach takes advantage of the unique conditions that exist within the body shortly after a stem cell transplant. "It usually takes several months following a transplant for the new tissue to take root in the bone marrow and fully reconstitute the blood supply," said Soiffer, who is also a professor of medicine at Harvard Medical School. "The period while that reconstitution is taking place is special. The initial chemotherapy has depleted much of the patient's immune system, and the body is trying to restore its previous state of function. That 'unsettled' condition seems to be a very opportune moment for an intervention such as a cancer vaccine."

One of the pleasant surprises of the study was that GVHD rates among study participants varied little from those of transplant-only patients. As part of the transplant process, patients receive Tracrolimus, a medication that inhibits the newly implanted tissue from launching an immune system attack on the recipient's body. Researchers speculated that the

drug might dampen the vaccine's ability to spark an immune response against diseased cells, but that turned out not to be a problem.

Researchers also have strong evidence that the transplant and vaccine complement each other in fighting AML and myelodysplasia cells. By analyzing the blood of patients who received the combined therapy, investigators found a sharp drop in a telltale protein, indicating cancer cells were being killed by the immune response triggered by the vaccine.

The study, though small in size, provides a solid indication that the future of cancer therapy may involve combinations of treatments -- such as chemotherapy, radiation, and surgery -- that directly kill cancer cells, and other agents -- such as cancer vaccines - that mobilize the immune system against the malignancy. "Where we currently have effective cancer therapies, they almost always involve the combination of treating the disease and the host," said Dranoff, who is also an associate professor of medicine at Harvard Medical School. "Chemotherapy and 'smart' drugs have a crucial role to play, but when cancer cells find a way around them, immune-based treatments offer another line of defense."

Source: Dana-Farber Cancer Institute