New Approach Could Make Bone Marrow Transplants Safer, Stronger

Tests prevented relapse and limited graft-vs.-host disease (GVHD) in laboratory models of leukemia and multiple myeloma.

November 7, 2022 By Fred Hutch News Service and Sabrina Richards

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Bone marrow transplants have transformed care for patients with blood cancers because donated immune cells often prevent cancer relapse by killing off residual malignant cells. One of the drawbacks of the treatment is graft-vs.-host disease — a common side effect that occurs when the transplanted cells see the recipient's healthy tissues as foreign and attack them. These attacks can be short-lived and mild, or chronic, debilitating and even deadly.

Since bone marrow transplantation was developed at Fred Hutchinson Cancer Center, scientists been working to devise strategies that boost the tumor-fighting capacity of donated immune cells without making GVHD worse.

Now, a Fred Hutch team has developed a two-hit, post-transplant approach that clears away the immune cells underpinning GVHD, then boosts the anti-tumor activity of the immune cells left behind. In work published October 14 in Science Immunology, the team showed the approach prevented relapse in laboratory models of bone marrow transplantation to treat leukemia and multiple myeloma.

"We found that we could dramatically improve the anti-leukemia or anti-myeloma effects [of a transplant] while abrogating GVHD," said study lead Dr. Geoff Hill, who heads Fred Hutch's Immunotherapy Integrated Research Center and holds the José Carreras/E. Donnall Thomas Chair for Cancer Research. "The new findings help define why some tumors respond [to bone marrow transplant] and some don't."

The strategy, which has so far only been tested in mice, employs a drug already in use to prevent GVHD, plus an experimental compound that improves on a naturally immune-stimulating molecule. Postdoctoral fellow Dr. Simone Minnie, who spearheaded the project, also identified the key group of immune cells that's activated by her strategy.

"The implication is, as we're using more modern approaches to prevent GVHD, we really need to think about how to improve anti-leukemic effects in a different way than we traditionally do," said Hill, who also cares for patients with blood cancers.

Delving Deeper Into Bone Marrow Transplant

The new GVHD-avoiding strategy grew out of a different question, said Minnie: “Why do some blood cancers respond to bone marrow transplant while others don’t?”

Many patients with leukemia, for example, can be cured with donated bone marrow or blood stem cells in an allogeneic transplant. But the procedure is much less successful against multiple myeloma, a cancer of the cells that produce antibodies. (Multiple myeloma patients more often undergo autologous transplantation, receiving back their own stem cells after chemotherapy clears the cancer.) Minnie wanted to understand why the two types of tumor react so differently to donated, or allogeneic, blood stem cell transplantation.

She focused on T cells, a specialized type of immune cell that can recognize infected or diseased cells — including cancer cells — and kill them. Many of today’s cancer immunotherapies take advantage of T cells’ anti-tumor capabilities: Checkpoint inhibitors seek to remove the restraints that keep activated T cells from attacking cancer, while cell-based immunotherapies use laboratory-engineered T cells to kill off leukemias and lymphomas.

T cells are among the donated immune cells that kill off blood cancer cells after a bone marrow transplant. This is because they see the cancer cells, derived from a different person, as foreign and dangerous. Unfortunately, healthy tissue can also look dangerous to donated T cells, which leads to GVHD.

Minnie suspected that a phenomenon called T-cell exhaustion might be at the root of multiple myeloma’s ability to resist the anti-cancer activity of donor T cells. If T cells don’t eliminate their target cells quickly, they become less effective as the fight drags on. (This is built into the system: The body needs ways to ramp down excessive inflammation to limit its damage.)

Perhaps, Minnie hypothesized, myeloma exhausts T cells in a way that leukemia doesn’t.

To compare and contrast tumor types that either resist or are susceptible to bone marrow transplantation, Minnie developed mouse models of bone marrow transplantation for myeloma and leukemia.

Directing T Cells Toward the Cancer

T cell activity is modulated by a system of molecular “gas pedals” and “brake pedals.” The gas pedals promote T-cell activity against target cells, while brakes rein the cells in. It’s a two-step process: once a T cell expresses a gas pedal or brake, it also needs a specific molecular cue (called a ligand) from the T cell’s environment to rev it up or slow it down.

Minnie discovered that multiple myeloma cells expressed much higher levels of the ligands that hit the T cells’ brakes than leukemia cells. This helped explain why, even though all donated T cells

had a lot of brakes, the immune cells could still effectively attack leukemia cells.

T cells that cause GVHD are revved up and seeing targets everywhere. And healthy tissue, unlike myeloma cells, doesn't do much to slow them down. Minnie did see what appeared to be exhausted T cells after transplant to treat myeloma — but they had worn themselves out by tilting at healthy tissue, not cancer cells. In fact, Minnie found that using a checkpoint inhibitor to remove T cell brakes just exacerbated GVHD without improving T-cell activity against myeloma cells.

So Minnie dosed mice with a drug called cyclophosphamide, which is used after bone marrow transplant to prevent or limit GVHD. Cyclophosphamide kills rapidly dividing cells, like the highly activated T cells attacking healthy tissue.

"What we saw was that all those T cells that express really high levels of those inhibitory receptors — wiped out," Minnie said. "Unfortunately, that also means you've wiped out the bulk of your T cells."

The myeloma relapsed after cyclophosphamide treatment. But this time, the exhausted-looking T cells that Minnie detected recognized only tumor cells, not healthy tissue.

"And that's what you see in a solid tumor setting, where if you use checkpoint inhibition or immunotherapy to target that T-cell exhaustion, you can get [tumor] control," Minnie said.

But that didn't work in Minnie's multiple myeloma transplant model: Cancer returned whether the mice received checkpoint inhibitors or not.

Minnie found that the T cells left behind by cyclophosphamide were a special type, called stem-like central memory T cells. These have the capacity to fuel a potent, long-lasting anti-tumor response — but they were sitting in neutral.

In this case, Minnie said, giving checkpoint inhibitors is "like taking your foot off the brakes when you're sitting on a flat road: nothing happens."

Minnie needed to hit the T cells' gas pedals instead of removing their brakes. She and Hill turned to Dr. Aaron Ring, a collaborator at Yale University. Ring had developed a synthetic form of a molecule called IL-18. Though IL-18 can stomp on T cell's gas pedals, tumor cells produce high concentrations of an IL-18-jamming protein, leaving T cells sputtering. Ring and his team tweaked IL-18 so that it cannot be jammed by the "decoy" target but can still rev up T cells, dubbed decoy-resistant IL-18.

Minnie found that she could make bone marrow transplantation work against multiple myeloma — and even more effective against AML — when she followed post-transplant cyclophosphamide with decoy-resistant IL-18. The experimental compound boosted the anti-tumor cells left in the wake of cyclophosphamide, enabling an anti-cancer attack without enabling GVHD.

A similar type of memory T cell has been seen in people who have received post-transplant

cyclophosphamide, and we could show that these cells expressed the receptor for IL-18 after transplantation, Minnie said.

“But putting those two things together and going, ‘Hey, why don’t we try to target these with an agonist [activating] immunotherapy?’ That’s new,” she said.

Broadening Transplant Horizons

Hill and Minnie are working to see if their success in mice will translate to patients in the clinic; they’re also digging into the biology behind the findings. Ring’s spinout company, Simcha Therapeutics, is testing decoy-resistant IL-18 in an early-stage trial against solid tumors. With Ring, Hill and Minnie have filed a provisional patent for their approach.

If the strategy proves successful, it could be more readily available than more-complicated forms of immunotherapy, Minnie said. Decoy-resistant IL-18 does not need the specialized production facilities required to produce, for example, engineered T cells because it is a recombinant protein. That also means it could be available and administered — along with cyclophosphamide — to patients in smaller or rural hospitals.

The team is also exploring whether other immune-activating compounds could work as well — or even better — to activate a bone marrow transplant’s anti-cancer potential without also triggering GVHD. Minnie is also working to better understand the T cells her strategy activates, including figuring out what they are targeting on cancer cells.

They are also investigating whether the basic approach — strategically giving the right T cells gas rather than taking away their brakes — could work in other transplant or cellular immunotherapy contexts.

“There are broad immunotherapy implications,” Hill said.

This work was funded by the National Cancer Institute, the American Society for Transplantation and Cellular Therapy and the Klorfine Foundation.

Note: Scientists at Fred Hutch played a role in developing these discoveries, and Fred Hutch and certain of its scientists may benefit financially from this work in the future.

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