How a New Approach Transformed Bone Marrow Transplants and Graft-Vs.-Host Disease

A Fred Hutch expert on bone marrow transplants reflects on recent lifesaving successes in the field and where research is headed.

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Fred Hutch Cancer Center opened its doors 50 years ago, founded by the team that made bone marrow transplantation (BMT) a reality. Since the breakthroughs in the late 1960s that showed the Nobel Prize-winning treatment for blood cancers and other blood disorders could save lives, Fred Hutch researchers have worked to make BMT more effective and safer for patients.

Now, more than 1.5 million transplants have been performed worldwide. The field's successes mean that today's transplant experts are working in a very different landscape than even 10 or 15 years ago, said Fred Hutch's Director of Hematopoietic Stem Cell Transplantation Geoffrey Hill, MD, FRACP, FRCPA.

"I can't remember the last time I saw someone with bad gut graft-vs.-host disease," said Hill, who also directs Fred Hutch's Translational Science and Therapeutics Division and holds the Leonard and Norma Klorfine Endowed Chair for Clinical Research. "We still see chronic GVHD, but we don't see that penetrance of severe disease and people dying of GVHD."

GVHD, or graft-vs.-host disease, is a transplant complication in which donor immune cells called T cells attack host tissue. It can range from mild and temporary to life-threatening and chronic —

but the deadly, debilitating cases are rare now. As Fred Hutch's 50th anniversary year winds down, Hill chatted about the recent advancements that made this possible, and where BMT researchers are focusing next.

What interested you in bone marrow transplant as a young physician?

When I started in the 1990s, transplant was the first frontier of oncology treatment. There were significant cures. Of course there were still relapses, but nevertheless we could see people that were living long term, having had what was otherwise a fatal disease.

Hematology was ahead of the rest of the cancer fields in relation to understanding how the cancer

process was working and what was driving it from a genetic point of point of view. It was at the leading edge — and still is — and there was quite a dynamic feeling.

What were the challenges that BMT researchers were tackling back then?

Despite the fact that BMT could cure cancer, we still lost 30 to 40% of people from transplant-related mortality, mainly graft-vs.-host disease and infection. Fungal infections were a big problem, and the drugs available were very toxic. For example, we could use amphotericin for only a limited time because it caused renal failure and other issues within a couple of weeks.

In the 2000s, we started to get good anti-fungal agents that weren't as toxic. The advent of new orally active anti-fungal agents really changed the field from an infection point of view, and we also got better at managing viral infections.

But we still had the issue of people getting life-threatening GVHD that we couldn't treat. That really started to change around 2015, when we started to treat people on clinical studies with post-transplant cyclophosphamide or some of the graft-engineering approaches [that remove some donor T cells] that Marie Bleakley [holder of the Gerdin Family Endowed chair for Leukemia Research] here, and others elsewhere, have been pioneering.

How did oncologists try to prevent GVHD before scientists started testing cyclophosphamide?

Previously, the way we prevented GVHD was by using a calcineurin inhibitor like cyclosporin or tacrolimus, and an anti-metabolite like mycophenolate or methotrexate. Those agents suppress T-cell function, but they don't remove the offending T cell.

There's some data now that what they actually do is rescue the alloreactive, disease-causing T cell that will cause GVHD, salvaging the cell to reappear at a later time point when you start removing immunosuppression. Historically this is what we would see: We used to take people off their cyclosporin and tacrolimus and most would develop chronic GVHD.

What makes post-transplant cyclophosphamide different?

With post-transplant cyclophosphamide, you don't use the same immune-suppressive regimen when you do the stem cell transplant. Historically, we'd start the immunosuppression two or three days before the graft. Now, we do nothing.

And of course, the donor T cells see the recipient and go crazy — and vice versa [the recipient T cells react to donor cells]. There's this big in vivo response of donor versus host and the T cells start expanding and making cytokines [immune-activating molecules].

And on day three or four, you give a large dose of cyclophosphamide, and you preferentially kill the cells that are reacting to each other. So unlike with cyclosporin, where you're probably just salvaging the cells to fight another day, with post-transplant cyclophosphamide, you're killing them.

Other researchers had tried something similar by just removing all the T cells, but we know that if

you do that, while you do prevent GVHD, people get overwhelming infections and they also tend to relapse. We don't see higher rates of relapse with post-transplant cyclophosphamide, although early infection is an issue in many studies.

What kind of transplant settings has post-transplant cyclophosphamide been tested in?

We use it in almost every transplant setting, other than cord blood transplant, and it works in all scenarios tested to date. The idea of using post-transplant cyclophosphamide came from Johns Hopkins, but several Fred Hutch groups have contributed to the work that has changed the standard of care. Marco Mielcarek did one of the first studies of post-transplant cyclophosphamide in 2016.

I was involved in a study in Australia using intensive, myeloablative conditioning in people getting transplants from a matched sibling, using post-transplant cyclophosphamide and really pulling back on the other immune suppression that's typically given. We saw that there was a dramatic reduction in GVHD and an improvement in relapse-free survival as well. And we didn't see an infectious signal that other studies have seen.

Brenda Sandmaier and Masumi Oshima recently completed another prospective study here where they've looked at giving more intensive immune suppression versus post-transplant cyclophosphamide in a group of patients getting low and reduced-intensity conditioning before the transplant. Their study used unrelated donors and post-transplant cyclophosphamide with two subsequent agents, cyclosporin and sirolimus (versus cyclosporin, sirolimus and mycophenolate). They saw that the rates of chronic GVHD were dramatically different with the post-transplant cyclophosphamide.

There has also been a major study by the Center for International Blood and Marrow Transplant Research (CIBMTR) using unrelated donors with low- and mid-level conditioning intensity with post-transplant cyclophosphamide versus methotrexate and tacrolimus, and they showed a similar improvement with cyclophosphamide.

What makes post-transplant cyclophosphamide so great?

It's cheap and anyone anywhere in the world can do it. And it's so effective, it's really a universal standard of care now, at least in North America, against which other strategies will be compared. The bar for competing approaches is now high.

The one setting we don't use it in is cord blood transplant. Because the number of stem cells are already so low, we worry about exacerbating graft failure. There are also some patients who, because of age or certain (mainly cardiac) comorbidities, can't safely receive it.

Where's the research going next?

As far as post-transplant cyclophosphamide goes, some of the questions relate to what's the best immune suppression to use afterward. Do we need to use two or more agents, or can we pull back? And are there better agents to use now that might simplify management?

It is also not clear that the dose of cyclophosphamide we currently use is optimal. A number of studies, including at the Hutch, are now examining the effects of reductions in doses.

What we don't understand now, which is super interesting, is why — despite profound reductions in GVHD — we aren't seeing increased rates of relapse. And so that's where a lot of our research is focused now: How does post-transplant cyclophosphamide still allow an anti-leukemic effect to persist and how can we build on and improve that, since relapse is now overwhelmingly the major cause of treatment failure?

There are a number of approaches scientists are trying, like focusing on specific T cells or using certain growth factors. We think that for the T cells we've generated with this paradigm, there's not a lot of point in trying to take the brakes off their response, because we've already done that. You have to drive the graft-vs.-leukemia response. So we're trying to do that with specific cytokines that look very active in preclinical studies.

And there's also an opportunity to think differently about who can get a transplant. Most blood cancers occur in people who are 65 and older. In the past, it was about trying to make sure everyone's in complete remission before transplant, because we know they do better from a relapse point of view. But it's also clear that it's hard to get stringent complete remissions in patients who are older, because their disease is more resistant, and they additionally often can't tolerate very intensive therapy.

So the other brave new world that we can think about is whether we can take older people straight to transplant even with residual disease. As [Fred Hutch BMT experts] Fred and Jake Appelbaum said in a recent commentary, "in life, as in sports … put your best player on the field." And that's transplant.

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