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What it takes to survive a transplant

Many patients with blood cancers, such as multiple myeloma, leukemia, or lymphoma, have radiation treatment or chemotherapy to destroy their tumor cells and diseased bone marrow. Unfortunately the treatment damages their immune system leaving them immunocompromised. To restore their immunity patients may be transplanted with bone marrow from a healthy donor that will enable their body to make both red blood cells and all the white blood cells that are needed to restore the immune system. T cells are one broad category of white blood cells. These cells will actively seek out and destroy most or all of the remaining cancer cells.

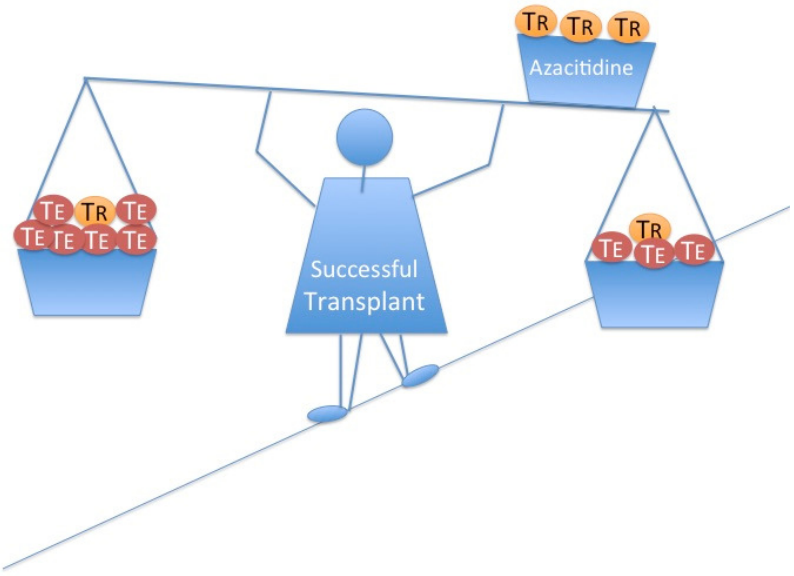

Fig. 1. By altering the balance of T effector (TE) and T regulator (TR) cells azacytidine may result in more patients surviving bone marrow transplantations that leave them both tumor free and without the side effect of graft versus host disease.

Patients may be surprised to learn that while bone marrow transplantation is the only curative therapy for some of these blood cancers, it carries the risk of a serious side-effect: graft versus host disease (GvHD). About 50% of transplant patients get mild to severe GvHD ranging from a limited mild rash or diarrhea to far more extensive and debilitating disease. For about 30% of these it can even be fatal. Our laboratory is one of many that is researching the underlying causes of this disease with the hope of reaping the benefits of a bone marrow transplant while minimizing or eliminating the risk of GvHD.

We know that both the benefits and risks of transplantation are caused by the donor's T cells. In most biological processes there are signals that cause specific actors to aggressively respond to a problem and other signals that cause regulators to dampen the response to keep it under control. For the immune system a balance between subsets of "T effector cells" and "T regulatory cells" often governs the response. T effector

cells proliferate rapidly when they encounter tumor cells so as to more effectively eradicate them. As the number of tumor cells decreases, healthy patient cells with a similar appearance are increasingly vulnerable to a mistaken attack and destruction. This results in GvHD.

All cell types in our bodies contain the same DNA blueprint. However, there are chemical modifications on the DNA that act like "marks" on this blueprint to tell individual cells which instructions to follow. We, and others, have previously published work that showed it is actually possible to convert T effector cells into T regulatory cells by administering the drug azacitidine to remove some of these marks. We have found that if we inject azacitidine into mice, only a small percentage get GvHD even though the T cells can still eliminate the tumor.

Because drugs sometimes have unforeseen side effects, it is always important to understand all the means by which a drug prevents a disease. This knowledge can be used to improve upon a treatment, understand the best circumstances for delivering treatment, develop additional treatments, or reveal other diseases or conditions in which the drug might be useful.

As published in the Journal of Immunology, we have now discovered another way that azacitidine prevents GvHD. Because T effector cells and T regulatory cells have differently marked DNA, azacitidine keeps T effector cells from proliferating, but has no such effect on T regulatory cells. Thus azacitidine can rapidly alter the balance of T effector and T regulatory cells.

This new information will help us as we design clinical trials testing the ability of azacitidine to prevent GvHD in cancer patients who receive bone marrow transplants. Timely administration of azacitidine, as in our mouse studies, might allow the transplanted effector cells to kill the leukemia and the transplanted regulatory cells to keep matters under control.

What it takes to survive a transplant may just be good balance.

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Publication

Azacitidine Mitigates Graft-versus-Host Disease via Differential Effects on the Proliferation of T Effectors and Natural Regulatory T Cells In Vivo.
Cooper ML, Choi J, Karpova D, Vij K, Ritchey J, Schroeder MA, DiPersio JF
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