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Mystery explained: How a common chemo drug thwarts graft rejection in bone marrow transplants

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Results of a Johns Hopkins study may explain why a chemotherapy drug called cyclophosphamide prevents graft-versus-host (GVHD) disease in people who receive bone marrow transplants. The experiments point to an immune system cell that evades the toxic effects of cyclophosphamide and protects patients from a lethal form of GVHD.

The findings, published online Nov. 13 in *Science Translational Medicine*, could pave the way for improvements in preventing GVHD and rejection of transplanted bone marrow and new therapies to prevent or treat a relapse of the underlying cancer after a transplant.

"Finding the optimal conditions to avoid interfering with immune cells working to eradicate cancer while preventing graft rejection and GVHD is the holy grail of bone marrow transplant," says Leo Luznik, M.D., associate professor of oncology at the Johns Hopkins Kimmel Cancer Center. "We've known for some time that giving cyclophosphamide after a transplant helps prevent GVHD, and our study provides an important piece of the puzzle for why it works."

GVHD occurs when newly transplanted immune cells from a donor's bone marrow attack the patient's body. Commonly used immunosuppressant drugs prevent rapid-onset, acute GVHD but not persistent, long-lasting, chronic GVHD, which may cause severe disability and death.

In the early 2000s, Johns Hopkins scientists Leo Luznik and Ephraim Fuchs found that giving patients high doses of cyclophosphamide – a drug derived from nitrogen mustard and used to treat blood cancers – three days after bone marrow transplant successfully thwarts acute and chronic GVHD. Johns Hopkins physicians also found that post-transplant cyclophosphamide enabled safe administration of new, half-matched bone marrow transplants in addition to traditional, fully matched ones. Medical centers around the world now use the Johns Hopkins protocol of post-transplant cyclophosphamide, and Luznik says the inexpensive drug is becoming increasingly mainstream in bone marrow transplant regimens.

Some of the first clues to how cyclophosphamide works were also discovered in the 1980s by Johns Hopkins scientists. They found that cyclophosphamide kills all of the donor's transplanted bone marrow cells except for stem cells containing high levels of an enzyme called aldehyde dehydrogenase (ALDH). The ALDH-laden stem cells evade the toxic effects of cyclophosphamide and rebuild the patient's immune system. Richard Jones, M.D., professor and director of the Bone Marrow Transplant Program at Johns Hopkins, developed a now commonly used assay to study ALDH levels in individual cells.

Yet, scientists lacked an explanation for why post-transplant cyclophosphamide effectively curtailed acute and chronic GVHD.

Luznik and his team inventoried types of immune cells present in the blood of bone marrow transplant patients treated with post-transplant cyclophosphamide. The scientists zeroed in on a type of immune cell called regulatory T-cells, which were known to suppress autoimmune responses. They found high levels of the regulatory T-cells in patients treated with post-transplant cyclophosphamide, and lab-cultured cells survived cyclophosphamide treatment.

Using polymerase chain reaction methods that amplify DNA and Jones' assay that detects by-products of ALDH, the Johns Hopkins team found that regulatory T-cells express high levels of ALDH.

"These regulatory T-cells are resistant to post-transplant cyclophosphamide and likely subdue the autoimmune-like response of the donor's bone marrow, preventing GVHD," says Christopher Kanakry, M.D., first author of the study and clinical fellow at the Johns Hopkins Kimmel Cancer Center. Patients receiving standard immunosuppressive drugs after transplant, as opposed to high-dose cyclophosphamide, have slower recovery of regulatory T-cells in their blood, adds Kanakry.

The scientists also showed, in lab-cultured human cells, that an ALDH-blocking drug strips regulatory T-cells of their ability to grow and protect themselves from cyclophosphamide.

Luznik says his team is continuing to study methods to improve post-transplant cyclophosphamide, and it may be possible to use these findings to add other relapse-fighting therapies early after transplant. "Our findings may also lead to even wider acceptance of post-transplant cyclophosphamide," he said.

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The assay (Aldefluor) used in this research was developed and patented by Richard Jones. Under a licensing agreement between Aldagen and the Johns Hopkins University, Jones is entitled to a share of royalties received by the University. The terms of this arrangement are managed

by Johns Hopkins University in accordance with its conflict-of-interest policies.

More information: "Aldehyde Dehydrogenase Expression Drives Human Regulatory T Cell Resistance to Posttransplantation Cyclophosphamide," by C.G. Kanakry et al. *Science Translational Medicine*, 2013.

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