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Stem cell transplant without radiation or chemotherapy pre-treatment shows promise

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Researchers at Dana-Farber/Boston Children's Cancer and Blood Disorders Center report promising outcomes from a clinical trial with patients with a rare form of bone marrow failure who received a hematopoietic stem cell transplant (HSCT) after pre-treatment with immunosuppressive drugs only. This is the first trial reporting successful transplant in dyskeratosis congenita (DC) patients without the use of any radiation or conventional cytotoxic chemotherapy beforehand.

The trial's data were presented by study authors Leslie Lehmann, MD, and Suneet Agarwal, MD, PhD, of Dana-Farber/Boston Children's, at the 56th annual meeting of the American Society of Hematology (abstract #2941). The data suggest that this immunosuppression-only approach could benefit patients with DC—and, perhaps, other bone marrow failure syndromes—who are at high risk of poor transplant outcomes because they cannot tolerate the toxicity of conventional or even reduced-intensity conditioning.

All four participants in the study are alive and well between 10 and 27 months after transplant. None remain dependent on transfusions to maintain blood counts, nor did any experience significant unexpected toxicities or infections during or after transplantation. Were it not for this new regimen, one patient would have been ineligible for transplant due to severe DC-related lung disease.

Conventional transplant conditioning employs radiation and/or high-dose cytotoxic drugs (also known as alkylators) to destroy the bone marrow

and blood and immune cells; it also causes widespread cellular damage throughout the body. The process prepares the patient's body to accept the donated stem cells, reducing the risk of rejection and providing a hospitable environment for the new cells to engraft, thrive and produce new blood and immune cells.

In DC and other bone marrow failure syndromes, however, the disease itself already weakens or destroys the patient's bone marrow, raising the question of whether a less toxic approach could effectively condition patients for transplant.

"These data show that it is possible to achieve engraftment within the context of DC using immunosuppression-only conditioning. This experience begs the question of whether we can think more broadly about this approach's applicability for other conditions, something I think is worth considering," Agarwal said.

"Bone marrow failure syndromes are problems of blood and immune cell production," he added. "In theory, then, in some of these conditions it should be possible for healthy donated stem cells to outcompete native cells, without exposing patients to the toxic effects of radiation or alkylating agents."

Eighty percent of patients with DC develop bone marrow failure before reaching age 30. The genetic defects underlying the disease prevent cells from maintaining their telomeres, the caps at the ends of chromosomes that gradually shorten as cells divide and a person ages. As a result, DC patients' hematopoietic stem cells age prematurely and do not divide well. While an HSCT can cure the resulting bone marrow failure, outcomes are often poor, likely because of the toxicity associated with conventional conditioning.

The cellular defects in DC created an opportunity for Agarwal and his

collaborators to attempt immunosuppression-only pre-transplant conditioning. Tamping down a patient's immune system, they theorized, would give donor stem cells and their progeny a chance to outcompete the patient's existing cells with a minimal risk of rejection. At the same time, avoiding radiation and alkylators—which cause widespread cellular damage throughout the body—should reduce the risk of long-term HSCT-related complications, such as organ failure and cancer.

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