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HIV drug reduces graft-versus-host disease in stem cell transplant patients

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An HIV drug that redirects immune cell traffic appears to significantly reduce the dangerous complication graft-versus-host disease (GvHD) in blood cancer patients following allogeneic stem cell transplantation (ASCT), according to new research from the Perelman School of Medicine at the University of Pennsylvania that will be presented today at the 53rd American Society of Hematology Annual Meeting. Standard GvHD treatments suppress the immune system, reducing – but not eliminating – the risk of developing the common problem. In the current trial, treatment with the HIV drug maraviroc dramatically reduced the incidence of GvHD in organs where it is most dangerous -- without compromising the immune system and leaving patients more vulnerable to severe infections.

"There hasn't been a change to the standard of care for GvHD since the late 1980s, so we're very excited about these results, which exceeded our expectations," says Ran Reshef, MD, an assistant professor in the division of Hematology-Oncology and a member of the Hematologic Malignancies Research Program at Penn's Abramson Cancer Center. "Until now, we thought that only extreme suppression of the immune system can get rid of GvHD, but in this approach we are not killing immune cells or suppressing their activity, we are just preventing them from moving into certain sensitive organs that they could harm."

Reshef and colleagues will present results showing that maraviroc is safe and feasible in ASCT patients – those who receive stem cells from a healthy donor -- and that a brief course of the drug led to a 73 percent

reduction in severe GvHD in the first six months after transplant, compared with a matched control group treated at Penn during the same time period (6 percent developed severe GvHD vs. 22 percent, respectively).

"Just like in real estate, immune responses are all about location, location, location," Reshef says. "Cells of the immune system don't move around the body in a random way. There is a very distinct and well orchestrated process whereby cells express particular receptors on their surface that allow them to respond to small proteins called chemokines. The chemokines direct the immune cells to specific organs, where they are needed, or in the case of GvHD, to where they cause damage."

Thirty-eight patients with blood cancers, including acute myeloid leukemia, myelodysplastic syndrome, lymphoma, myelofibrosis, and others, enrolled in the phase I/II trial. All patients received the standard GvHD prevention drugs tacrolimus and methotrexate, plus a 33-day course of maraviroc that began two days before transplant. In the first 100 days after transplant, none of the patients treated with maraviroc developed GvHD in the gut or liver. By contrast, 12.5 percent of patients in the control group developed GvHD in the gut and 8.3 percent developed it in the liver within 100 days of their transplant.

The differential impact of maraviroc on those organs indicates that the drug is working as expected, by limiting the movement of T lymphocytes to specific organs in the body. Maraviroc works by blocking the CCR5 receptor on lymphocytes, preventing the cells from trafficking to certain organs. The researchers saw no effect on skin GvHD, so they theorize that the CCR5 receptor might be more important for sending lymphocytes into the liver and the gut than for the skin.

After 180 days, the benefit of maraviroc appeared to be partially sustained in patients and the cumulative incidence of gut and liver GvHD

rose only to 8.8 percent and 2.9 percent, respectively. The cumulative incidence in the control group, however, remained higher, at 28.4 percent for gut and 14.8 percent for liver GvHD. Based on those data, the research team plans to try a longer treatment regimen with maraviroc to see if they could prolong the protective effect.

Maraviroc treatment did not appear to increase treatment-related toxicities in these patients, nor did it alter the relapse rate of their underlying disease.

David Porter, MD, professor of Medicine and director of Blood and Marrow Transplantation in the Abramson Cancer Center, and Robert Vonderheide, MD, DPhil, associate professor of Medicine and Associate Director for Translational Research at the Abramson Cancer Center, are the senior authors of the study.

Provided by University of Pennsylvania School of Medicine

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