Study suggests stem cell transplant survivors at increased risk of developing heart disease

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New research appearing online today in *Blood*, the journal of the American Society of Hematology (ASH), suggests that long-term survivors of hematopoietic cell transplants (HCT) are at an increased risk of developing heart disease risk factors such as high blood pressure, diabetes, and high cholesterol when compared to the general population. These risk factors, combined with exposure to pre-HCT therapy, contribute to a noticeably increased risk of heart disease over time.

HCT, the transplantation of blood-forming stem cells from the bone marrow, circulating blood, or umbilical cord blood, is the primary treatment option for many patients with blood disorders. The healthy transplanted stem cells replace patients' damaged cells that caused their illness. Advances in transplantation strategies have contributed to marked improvements in patient outcomes, resulting in a growing number of long-term transplant survivors, many of whom struggle with one or more chronic, post-transplant health conditions. Previous researchers have speculated that survivors' exposure to potentially heart damaging pre-transplant chemotherapy and radiation or treatment for a life-threatening transplant complication known as graft-versus-host-disease (GVHD) can increase their risk of developing heart disease and its associated risk factors. However, there have been limited data to validate the contribution of pre-conditioning chemotherapy or radiation and GVHD to the eventual development of heart disease in long-term HCT survivors.

"While we know that heart disease is a real concern for long-term HCT

survivors, small sample sizes and a lack of long-term follow up in previous studies have only allowed us to look at a small piece of the puzzle of how this chronic condition develops in these patients," said Saro H. Armenian, DO, MPH, the study's first author, Assistant Professor in the Division of Outcomes Research, and Medical Director of the Pediatric Survivorship Clinic in the Childhood Cancer Survivorship Program at City of Hope in Duarte, CA. "Our study sought to better determine the specific factors before and after transplant that can lead to heart disease in a large group of transplant recipients."

In order to more thoroughly evaluate heart disease risk and development in HCT recipients, Dr. Armenian and his team of researchers designed a retrospective study to evaluate factors that may affect a survivor's risk of developing high blood pressure, diabetes, and high cholesterol after HCT. These factors included transplant recipients' exposure to pre-transplant chemotherapy and radiation, conditioning therapy for HCT, their type of HCT transplant, and whether they developed and were treated for GVHD post transplant.

To better determine HCT survivors' incidence of high blood pressure, diabetes, and high cholesterol compared to the general population, researchers analyzed medical records of 1,885 patients who underwent a first-time HCT for a blood cancer at City of Hope between 1995 and 2004 and had survived at least one year. The National Health and Nutrition Examination Survey was used to generate expected heart disease risk factor rates for the general population.

Following their analysis, researchers found a higher prevalence of high blood pressure, diabetes, and high cholesterol in long-term HCT transplant survivors when compared to the general population. HCT conditioning with total body radiation was associated with a 1.5-fold increase in risk of developing diabetes and a 1.4-fold increase in risk of developing high cholesterol, regardless of HCT type, a finding that

validates previous reports from long-term childhood and adult HCT survivors. While the mechanism by which total body radiation increases the risk of diabetes and high cholesterol in HCT recipients is not clear, previous studies have shown that abdominal radiation may contribute to known heart disease risk factors such as insulin resistance and an increase in belly fat in conventionally treated cancer patients. This evidence suggests that radiation-induced pancreatic or liver injury may play a role in an HCT transplant survivor's development of heart disease by increasing their risk for heart disease risk factors.

Next, researchers assessed the role of transplant type on long-term HCT survivors' risk of developing key heart disease risk factors. After reviewing the data, researchers observed that those who had received transplanted stem cells from a donor (allogeneic HCT) were at a significantly higher risk of developing high blood pressure, diabetes, or high cholesterol after transplant than those who had received blood-forming stem cells from their own body (autologous HCT). Over the 10-year study period, 45.3 percent of allogeneic HCT recipients developed high blood pressure, 20.9 percent developed diabetes, and 50.5 percent developed high cholesterol; whereas only 32 percent, 15.9 percent, and 43.3 percent of autologous HCT recipients developed these same conditions, respectively. Transplant recipients who had undergone an allogeneic HCT and who had experienced GVHD had the highest risk of developing heart disease risk factors, researchers concluded; 54.7 percent of this group developed high blood pressure, 25.8 percent developed diabetes, and 52.8 percent developed high cholesterol.

Not only did more allogeneic than autologous HCT recipients develop these heart disease risk factors over this time period, but they also developed them more quickly. Allogeneic HCT recipients developed high blood pressure and high cholesterol both at a median time to onset of 2.5 months, compared with autologous HCT recipients who developed the same conditions at 3.7 years and 1.6 years, respectively.

Allogeneic HCT recipients also developed diabetes more than two years earlier than autologous recipients (1.2 year median time to onset for allogeneic HCT recipients vs. 3.3 years for autologous transplant recipients).

In addition to evaluating incidence rates of key heart disease risk factors in this large group of long-term HCT survivors, investigators also assessed their impact on survivors' subsequent development of heart disease. A total of 115 patients went on to develop heart disease at a median rate of four years after HCT. At 10 years post HCT, the cumulative incidence of post-HCT heart disease in all survivors was approximately 7.8 percent, with the rate exceeding 11 percent in the survivors with multiple heart disease risk factors. In those survivors with multiple heart disease risk factors and past exposure to cardiotoxic chemotherapy or radiation, the incidence rose to approximately 18 percent, demonstrating that certain pre-transplant therapeutic exposures compound HCT recipients' risk of developing heart disease.

"Our findings show that the process of receiving a stem cell transplant alone increases a recipient's risk of developing heart disease; however, the type of transplant and whether the recipient was treated for GVHD can also increase that survivor's heart disease risk as well," said Dr. Armenian. "The results of this study demonstrate the importance of intervention strategies that can help mitigate these modifiable heart disease risk factors in transplant recipients before and after transplant, and we hope they can serve as a basis for creating a predictive model to identify those patients at highest risk of developing heart disease."

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