Massey researchers aim to develop models that can predict complications from stem cell transplantation

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Researchers at VCU Massey Cancer Center's Bone Marrow Transplant Program have recently published findings from a phase 2 clinical trial that demonstrate lymphocyte recovery in related and unrelated stem cell transplant recipients generally falls into three patterns that are significantly associated with survival. This first-of-its-kind research continues the efforts of principal investigator Amir Toor, M.D., to understand the immune system as a dynamical system that can be modeled to improve stem cell transplantation.

"We began considering lymphocyte reconstitution following stem cell transplantation as similar to population growth models. So, we graphed the lymphocyte counts of our patients at various times following their transplant as a logistic function and observed distinct patterns that correlated with clinical outcomes," says Toor, the lead investigator of the study and hematologist-oncologist and member of the Developmental Therapeutics research program at VCU Massey Cancer Center. "Our goal is to use this data to develop models that can predict complications from stem cell transplantation. Then, we may be able to intervene at key points in times with appropriate clinical treatments that will make the most positive impact on patients' outcomes."

The study, recently published in the journal *Biology of Blood & Marrow Transplantation*, retrospectively examined lymphocyte recovery and clinical outcome data from a recent phase 2 clinical trial (Clinical trials.gov identifier - NCT00709592) in which 41 patients received a stem cell transplant from related or unrelated donors. As part of the clinical trial protocol, the patients underwent low-dose radiation therapy and received one of two different doses of anti-thymocyte globulin (ATG), an immune-modulating drug given to guard against graft-versus-host-disease (GVHD) before transplantation. GVHD is a condition where the donor's immune system attacks the recipient's body. Following transplantation, the researchers observed that the patients' lymphocytes recovered in one of three general patterns that correlated significantly with survival, relapse, GVHD and the need for further donor immune cell infusions to treat the cancer.

Group A experienced fast, early lymphoid expansion, culminating in a high absolute lymphoid count (ALC) within two months of transplantation. Group B experienced a slower, but steady lymphoid expansion that peaked much later than group A with a lower ALC. Group C experienced very poor lymphocyte recovery that demonstrated an early, but brief lymphoid expansion with a very low ALC. Group B had the best clinical outcomes with a survival rate of 86 percent, followed by group A with a survival rate of 67 percent and group C with 30 percent survival. Relapse rates between groups A and B were similar at 33 and 29 percent, respectively, while group C experienced a 90 percent relapse rate. GVHD was observed in 67 percent of patients in group A, 43 percent of patients in group B and 10 percent of patients in group C. Finally, adoptive immunotherapy with donor cell infusions was required for 13 percent of patients in group A, 21 percent in group B and 70 percent in group C.

The discovery of these patterns in lymphocyte recovery build on prior research by Toor and his team that supports the concept of the immune system working as a dynamical system. In 2013, the Massey Bone Marrow Transplant Program's research team and Massey researcher Masoud Manjili*, D.V.M., Ph.D., sequenced DNA from the T cells of 10 stem cell transplant recipients and their donors and found a fractal, self-repeating pattern in the participants' T cell repertoires. This discovery suggested that physicians could potentially sequence the DNA of patients after they undergo stem cell transplantation and predict potential GVHD complications based on the pattern in which their T cell repertoire is developing. Another study of the same participants in 2014 also used whole exome sequencing and found significant variation in minor histocompatability antigens (mHA, which are receptors on the cellular surface of donated organs that are known to give an immunological response in some organ transplants) between the donor-recipient pairs. This variation represents a large and previously unmeasured potential for developing GVHD for which conventional human leucocyte antigen (HLA) testing, the test that matches stem cell transplants with donors, does not measure. This large library of immune targets, in turn, can serve to drive immune complications of transplantation such as GVHD or graft rejection.

Currently, physicians use stochastic models to determine the probability of a patient developing GVHD based on HLA test results. Stochastic models are not precise because they estimate probability by allowing for random variation in one or more variables. Dynamical system modeling, on the other hand, would account for the key variables

influencing transplant outcomes and their evolution over time, allowing physicians to personalize therapy based on the extent of a patient's immune recovery following transplantation.

"We've uncovered order in the structure of the immune system, we've found new variables influencing GVHD and we've now shown patterns in lymphocyte reconstitution that identify at-risk patients," says Toor. "Now, we are working to put it all together and develop a model of immune system reconstruction following stem cell transplantation that will allow physicians to make more informed treatment decisions."

Source:
Virginia Commonwealth University
