ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Targeting the Microbiome to Improve Outcomes in Stem Cell Transplant

Doris M. Ponce, MD
Associate Professor of Medicine
Hematologic Oncologist
Adult Bone Marrow Transplant
Memorial Sloan Kettering Cancer Center
New York, New York

H&O What are the characteristics of a healthy microbiome?

DP A healthy microbiome is dynamic and diverse. It consists of many different types of commensal bacteria—predominantly strict anaerobes—that vary along the length of the gastrointestinal tract.

H&O Is the microbiome different in healthy people compared with those who have leukemia, lymphoma, or myeloma?

DP The microbiome in healthy people is distinct from that of patients with hematologic malignancies in the pretransplant setting, as was elegantly reported by Peled and colleagues in 2020 in the *New England Journal of Medicine*. Patients with hematologic malignancies are at increased risk for injury to the microbiome owing to exposure to several insults. For example, high-dose chemotherapy may cause mucositis and prevent patients from eating, and the use of broad-spectrum antibiotics can affect healthy gut microbiota commensals.

H&O Does the state of the microbiome predict outcomes in stem cell transplant?

DP Yes, microbiome health is associated with transplant outcomes, including transplant-related mortality, acute graft-vs-host disease (GVHD), and GVHD lethality.

H&O Does the microbiome change after stem cell transplant?

DP The intestinal microbiome changes after transplant. In the immediate post-transplant period after conditioning, when patients experience decreased appetite and diarrhea, a decrease in microbiome diversity is frequently observed. However, as patients start to recover and eat better, the microbiome improves as well. In their 2020 study in the *New England Journal of Medicine*, Peled and colleagues evaluated the intestinal microbiome changes of patients at transplant centers in 4 geographic locations. Stool samples were obtained prospectively among patients undergoing allogeneic hematopoietic stem cell transplant at the institutions. Samples were requested weekly, and a median of 4 samples were collected from each patient. The study analyzed data for 1362 patients who had at least 1 evaluable sample obtained no more than 30 days before the first transplant procedure. Stool samples were analyzed in the early post-transplant period. We found that microbiome dysbiosis was a common denominator across the world, and it occurred at approximately the same time—in the first 2 weeks following conditioning regimen.

H&O Do changes in the microbiome impact outcome?

DP Stem cell transplant recipients with a preserved intestinal microbiome have a lower risk of experiencing transplant-related mortality and of developing severe or lethal GVHD. Certain commensal bacteria have been demonstrated to be beneficial, such as *Blautia,* whereas *Enterococcus* expansion promotes GVHD.

H&O Can the intestinal microbiome serve as a biomarker to predict the onset of GVHD?

DP Dr Marina Burgos da Silva and I were the first authors of a study that evaluated the gut microbiome and GVHD. We evaluated stool samples that were taken before and after the onset of GVHD. We found that dysbiosis of the microbiome was more pronounced among patients with gut GVHD compared with patients who did not have GVHD and patients with GVHD limited to the skin and/or liver. We observed microbiome dysbiosis prior to GVHD onset. It might therefore be possible to use the intestinal microbiome health as a biomarker to predict GVHD, as well as to predict the likelihood of a response to treatment.

> In mice, high consumption of lactose products favors growth of *Enterococcus*, which could be harmful to the gut microbiome.

A current limitation is the turnaround time needed to obtain results from testing of stool samples. Currently, results are not available the same day. If progress in this field is observed, intestinal microbiome health may be used as a biomarker to predict transplant outcomes and GVHD.

H&O Are there ways to prepare the microbiome to optimize transplant outcomes?

DP This question is tricky. The diet should be balanced and rich in all nutritious food groups. It is important for patients to continue to eat and drink. Patients who are unable to eat or drink have the least healthy microbiome.

Emerging data suggest that excessive ingestion of lactose products could be detrimental to the microbiome. In mice, high consumption of lactose products favors growth of *Enterococcus*, which could be harmful to the gut microbiome. This association is based primarily on mice models, along with retrospective data in humans. Further prospective evaluation is needed to further elucidate this question.

H&O Could you discuss your study of SER-155?

DP SER-155 is an ecobiotic capsule being developed by Seres Therapeutics that contains a group of healthy bacteria commensals selected for their properties. These bacteria appear to have a positive effect in the gut, according to preclinical and clinical data. They may favor healthy microbiome byproducts as well, such as the short-chain fatty acids that include propionate and butyrate. I am the principal investigator of this multicenter, prospective clinical trial. The primary objective of the study is to evaluate the safety and feasibility of SER-155 in patients undergoing allogeneic stem cell transplant. Secondary objective include assessment of infection rates and GVHD. Patients enrolled in the trial will receive 2 treatment courses consisting of 4 days of oral vancomycin for microbiome conditioning followed by 10 days of daily oral treatment with SER-155. The first course is administered pre-transplant, before the start of the conditioning regimen. The patients receive the second course after neutrophil engraftment. Additionally, there is an optional third treatment course if patients are exposed to broad-spectrum antibiotics up to 90 days after transplant. The trial is currently open and accruing patients.

H&O Are there any other strategies to target the microbiome in stem cell transplant?

DP The older strategy is fecal microbiota transplant. SER-155 can be considered version 2.0 of fecal transplant. Rather than transferring beneficial bacteria through a stool sample, the SER-155 capsule contains a reproducible type and amount of bacteria commensals that are deemed beneficial. Fecal microbiota transplant has been used in patients with corticosteroid-refractory acute GVHD. Additionally, other studies have evaluated the use of stool capsules to prevent and treat GVHD. To my knowledge, most of these studies are evaluating treatment in patients with corticosteroid-refractory gut GVHD, rather than newly diagnosed GVHD.

The field is evolving as researchers learn more about why bacteria and their byproducts are critical to humans, and how different types of bacteria interrelate. We are

still in the initial steps of learning how to optimize the microbiome. The next 5 years should bring more data to help further our understanding of how to harness the microbiome to customize treatment for patients.

Disclosure

Dr Ponce has served as consultant to Kadmon Corporation/ Sanofi, Evive, CareDx, Incyte, and Ceramedix, and has received research funding from Incyte.

Suggested Readings

Biernat MM, Urbaniak-Kujda D, Dybko J, Kapelko-Słowik K, Prajs I, Wróbel T. Fecal microbiota transplantation in the treatment of intestinal steroid-resistant graft-versus-host disease: two case reports and a review of the literature. *J Int Med Res*. 2020;48(6):300060520925693.

Burgos da Silva M, Ponce DM, Dai A, et al. Preservation of fecal microbiome is associated with reduced severity of graft-versus-host disease [published online August 15, 2022]. *Blood*. doi:10.1182/blood.2021015352.

DeFilipp Z, Hohmann E, Jenq RR, Chen YB. Fecal microbiota transplantation: restoring the injured microbiome after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplan*t. 2019;25(1):e17-e22.

Ilett EE, Jørgensen M, Noguera-Julian M, et al. Associations of the gut microbiome and clinical factors with acute GVHD in allogeneic HSCT recipients. *Blood Adv*. 2020;4(22):5797-5809.

Kaito S, Toya T, Yoshifuji K, et al. Fecal microbiota transplantation with frozen capsules for a patient with refractory acute gut graft-versus-host disease. *Blood Advances.* 2018;2(22):3097-3101.

Kakihana K, Fujioka Y, Suda W, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. *Blood.* 2016;128(16):2083-2088.

Markey KA, Schluter J, Gomes ALC, et al. The microbe-derived short-chain fatty acids butyrate and propionate are associated with protection from chronic GVHD. *Blood*. 2020;136(1):130-136.

Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382(9):822-834.

Ponce DM, Lombardo MJ, Ford CB, et al. A phase 1b study to evaluate safety, tolerability, pharmacokinetics, and efficacy of SER-155 in adults undergoing hematopoietic stem cell transplantation to reduce the risk of infection and graft versus host disease (NCT04995653) [ASCO abstract TPS7074]. *J Clin Oncol*. 2022;40(16 suppl).

Stein-Thoeringer CK, Nichols KB, Lazrak A, et al. Lactose drives *Enterococcus* expansion to promote graft-versus-host disease. *Science*. 2019;366(6469):1143-1149.

Taur Y, Coyte K, Schluter J, et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. *Sci Transl Med.* 2018;10(460).