Impact of microbiota on pathophysiology of graft-versus-host disease post allogeneic hematopoietic stem cell transplantation: a review

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***Abstract*: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially lifesaving treatment of patients with hematopoietic malignancies. Graft-versus-host disease (GVHD) becomes a main contributor to mortality as the T-cells from the donor recognize the host tissue as foreign. The intestinal microbiota remains severely affected after allo-HSCT resulting in loss of microbiota diversity and growth of opportunistic pathogens belonging to the Enterococcus genus. The disruption of the microflora along with occurrence of harmful pathogens results in high mortality from GVHD, organ failure and infection after allo-HSCT treatment. According to the recent studies and their findings, injury in the microbiota was globally observed after allo-HSCT treatment. Enterococcus colonization in the intestines is promoted by dietary habits like consumption of lactose post transplantation, making it a source of various bloodstream infections and accelerating GVHD. Recent reports suggest Enterococcus expansion in the presence of lactose, which is associated with an increase in GVHD related post allo-HSCT mortality. Moreover, severity of GVHD is also linked with changes in the fecal and plasma microbiota-derived molecules. In this review, we discuss the role of microbiota diversity from clinical and mouse microbiota research contributing to the development of post-transplant complications and domination of the Enterococcus pathogen which would be an advancement to find whether modification of the microbiota may reduce chances of GVHD.**

***Keywords*: allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, microbiota, enterococcus, transplantation**

Introduction

Allogeneic hematopoietic cell transplantation (allo-HSCT) is a pre-eminent treatment choice for several hematopoietic malignancies that affect the blood, bone marrow and lymph nodes. Allogeneic HSCT is an established treatment in which patients receive infusion of healthy stem cells from a healthy donor after undergoing intensive chemotherapy or radiation therapy. These hematopoietic blood cells can further develop into all types of blood cells viz. erythrocytes, leukocytes and platelets. Following the allo-HSCT treatment, the major contributors to the overall mortality of 50% are relapse of primary malignancy, graft-versus-host disease (GVHD), bloodstream infections and transplant related mortality.[1] However, relapse remains the leading cause of deaths after allo-HSCT. Intestinal microbiota harbors a diverse population of anaerobic bacterias and is responsible for modulating systemic immune responses of the host. It is very well known that the gastro-intestinal tract is heavily impacted after allo-HSCT causing modifications in the intestinal flora and decreased microbial population[2]. It is a question whether the microbiota modulates GVHD in the mouse model, the immune response and the clinical outcomes in patients undergoing allo-HSCT. Many authors have written a thorough review on allogeneic hematopoietic stem cell transplantation. [1-2]

Intestinal Microbiota and infections

The intestinal immune system harbors anaerobic bacteria and modulates the immune system of the host. It is the first line of defence against potential pathogens. After undergoing allo-HSCT, the intestinal mucosa becomes injured resulting in domination of potential pathogens. [3] This increases the risk of bloodstream infections with *Escherichia coli* and *Klebsiella pneumoniae* in patients post-transplantation. Culture experiments conducted on patients after the stem cell transplantation confirmed presence of *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infection. [4] Many studies have been conducted in line with this hypothesis and colonization of such pathogens and gram negative intestinal presence have been confirmed after fecal sampling from a large cohort of 708 patients post-transplantation. [5] It was found that on exposure of fluoroquinolone the gram negative bloodstream infection reduced significantly. However, it was observed that results in drug resistance in *Escherichia coli* bacteria.

Practice of broad-spectrum antibiotics can result in mortality after allo-HSCT. [6] It is still a debate whether prescribing such for preventive measures and use of such antibiotics is beneficial or risky. Considering the evidence and data, it is clear that use of such antibiotics results in post-transplant GVHD and GVHD related mortality. Interestingly, making use of prebiotics and probiotics support and sustain the microbiota to promote microbiota balance and to remain healthy. [7-8] Further studies that make use of such healthy microbiota promoting agents to assist in healing or modification of the injury after stem transplantation can be explored. With improved technology to understand the composition of the microbiota including the beneficial bacteria and fungi in the gut, there is enough evidence to support microbiota's impact on the development of the complications that arise after patients undergo allogeneic stem cell transplantation.

Intestinal microbiota and GVHD related mortality

It is hypothesized that the diversity of the gut microbiota is influenced by various factors like diet, use of antibiotics, infections etc. Geographical and cultural differences affect the features of the intestinal flora. It was first proposed in 1970 to determine the impact of microbiota on GVHD progression when it was found that the mice kept under germ-free condition had lowered incidence of GVHD. A multi-centre, retrospective study recruited 1362 allo-HSCT patients and collected 8767 stool samples to determine the correlation between the microbiota and the clinical outcomes. [9] Enterococcus genus was observed along with the loss of diversity suggesting intestinal injury. Fecal samples at peri-engraftment [10] at day 7-21 indicated a lower rate of GVHD related mortality. Subsequently, the fecal sample at baseline predicted poor survival compared to healthy volunteers.

In another study, a group of 141 allograft recipients derived a risk score of grade III-IV acute GVHD and out of four bacterial families, *Lachnospiraceae* was found in abundance. [11] This study observed a lower incidence of GVHD in the presence of *Lachnospiraceae*. [12] These findings are consistent with other studies. [13] Belonging to the same strain as *Lachnospiraceae*, *Blautia* [14] producta releases a protein called lantibiotic which is associated with lower GVHD related mortality. This is simply a reproducible observation of the microbiota in allo-HSCT patients and it is not known whether *Blautia* is an immunosuppressant or if it directly suppresses GVHD by devitalizing Enterococcus.

Microbiota and Graft-versus-host disease Pathogenesis

GVHD is caused when the donor T-cells recognize the host antigens as foreign and activate an autoimmune-like response to the recipient's body. [15] Acute GVHD includes the skin, Gastrointestinal, liver etc. whereas, chronic GVHD is widespread to other organs like lungs. The host undergoes further accelerated immune activation when the lymphocytes undergo activation and the CD4+ T cells [16-17] along with the T-helpers secrete cytokines. This is responsible for direct attack on the cells and organs such as skin, liver, gut which is very typical of GVHD injury. The intestinal epithelial cells impose an antigenic action on the donor T-cells by TRIP signalling pathway which is induced by microbial signalling. [18] Studying the same group for the effect of peri-transplant gut microbiota on GVHD by using microbiota of mice deficient in IL-17RA, exhibited an increase in the incidence of GVHD. [17]

Nutrition and Graft-versus-host disease

Considering the poor nutritional status of the patient post allo-HSCT, supplemental feeding is administered parenterally to sustain the nutritional levels of the patient. [20] This way the nutrients avoid the gut epithelium. Although this could possibly lead to changes in the composition of the microbiota due to insufficient levels of nutrients during stem cell transplantation and GVHD. More attention is given to the use of prebiotics and probiotics to treat this microbial imbalance, also called dysbiosis. Prebiotics can alter the composition of the microorganisms present in the gut. They are foods that induce beneficial activity of the microorganisms like bacteria and fungi whereas, probiotics contain defined amounts of microorganisms like yeast and good bacteria that are beneficial to the host's microbiota. Only a few studies have demonstrated the effect of prebiotics and probiotics in the allo-HSCT due to major safety issues [21-22], although this could possibly be a new area to study safety and efficacy of therapies in a clinical setting.

Conclusion

The stability of intestinal microbiota has an impact on the GVHD and other outcomes after allo-HSCT. Variation in diet, lifestyle, culture and environmental factors has an effect on the intestinal microbiota composition. Loss of the anaerobic microbiota may result in worse GVHD and increase mortality post-transplantation. Preclinical studies suggest that manipulating the gut can either improve or worsen GVHD. Although the relationship between the microbiota and the clinical outcomes still remains unexplained as there are many factors that influence the relationship between the intestinal microbiota and the clinical outcomes. Additional experiments are required for better assessment of the microbiota function and determine strategies in clinical practice. This may reduce the post-transplant GVHD and prevent bloodstream infections after allogeneic stem cell transplantation. Advancing in diagnostic techniques and understanding the ecology of the microbiota will help in developing better strategies to overcome GVHD complications.

Abbreviations

Allo-HSCT: Allogeneic hematopoietic stem cell transplantation. GVHD: Graft-versus-host disease.

Conflict of Interest

Authors affirm no conflict of interest to declare.

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