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Gut microbiota and its role in cancer patients

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ABSTRACT

Chemotherapy and allogeneic stem cell transplant suppress the body's immunity making them more prone to neutropenic sepsis, for which the patients have to be given broad-spectrum antibiotics. These antibiotics disrupt the well-organized colony of our intestinal microbiome creating dysbiosis. Dysbiosis makes the intestine a favorable platform for certain Gram-positive bacilli to proliferate which is *Clostridium difficile*. Traditional treatment requires the patient to take metronidazole, vancomycin, and probiotics. Recurrent *C. difficile* infection makes the traditional treatment a failure. Thus, fecal microbial transplant is the answer to recurrent *C. difficile.*

Key words: Allogeneic-hematopoietic stem cell transplant, *Clostridium difficile*, Chemotherapy, Dysbiosis, Fecal microbiota transplantation

Introduction

Cytotoxic drugs target rapidly dividing cancer cells and induce apoptosis; however, these agents often have low specificity for cancer cells and also damage other rapidly proliferating healthy host tissue. Many chemotherapeutic agents infiltrate the bone marrow and decreased white blood cell counts, in particular, neutrophils, putting patients at increased risk of bacterial infection.[1] As a result, antibiotic prophylaxis is recommended in high-risk patients to prevent neutropenic sepsis.

Analysis of stool specimens from allogeneic-hematopoietic stem cell transplant (allo-HSCT) recipients showed that broad-spectrum antibiotic administration was associated with perturbation of gut microbial composition. Studies in mice also demonstrated aggravated graft-versus-host disease (GVHD) mortality with broad-spectrum antibiotics use and led to a loss of the protective mucus lining of the colon, compromised intestinal barrier function, as well as increased a commensal bacterium with mucus-degrading capabilities, raising the possibility that mucus degradation may contribute to murine GVHD.[2]

Recent research supports the use of caution in prescribing prophylactic antibiotics with chemotherapy, as antibiotic administration may disrupt the complex interplay between the microbiota and the immune response to cancer.

Role of microbiome in our body

Gut microbiota plays a key role in maintaining homeostasis in the human gut. The gut microbiota, made up of trillions of microorganisms that colonize the distal digestive tract, is required for the development and persistence of a healthy immune response.[3] Intestinal immune maturation is dependent on the presence of commensal bacteria for the development of Peyer's patches, secretion of functional immunoglobulin A.[4] An individual's gut microbiota influences the body's ability to extract dietary calories and how these calories are used and stored. Gut bacteria have also been shown to influence the mature immune system by conditioning mononuclear phagocytes and shaping T-cell responses in the intestine. Next-generation sequencing has allowed scientists to characterize the composition of the gut microbiota on an individual level and has revealed that gut bacterial communities differ significantly between healthy and diseased individuals.[5] Intestinal bacteria can modulate the risk of infection and GVHD after allo-HSCT. Alterations are done in the normal microbial ecosystem which predisposed to *Clostridium difficile* infection (CDI) and gut inflammatory disorders such as inflammatory bowel disease (IBD). Currently, a large body of research exists demonstrating the association between an abnormal microbiota – termed dysbiosis – and the development of various types of cancer including oral squamous cell carcinoma, pancreatic cancer, and colorectal cancer.[6]

C. difficile and what it does?

C. difficile is a Gram-positive rod-shaped bacterium that can exist in a vegetative or spore form. Spores of *C. difficile* are resistant to high temperatures, ultraviolet light, harsh chemicals, and antibiotics. CDI is the predominant cause of antibiotic-associated diarrhea, ranging in severity from mild diarrhea to death.

CDI is one of the most common hospital-acquired infections and represents a major health problem in the United States.[7]

Among the most vulnerable populations susceptible to CDI are HSCT recipient,[8] where the incidence of CDI is as high as 25%. Vancomycin, metronidazole, and fidaxomicin are the first-line therapies for CDI; however, for hematopoietic cell transplantation patients, recurrent infection is common on cessation of antibiotic therapy, with severe cases being accompanied by a high incidence of mortality. Probiotic therapy, particularly using the yeast *Saccharomyces boulardii* in combination with high-dose antibiotic therapy, has been used for recurrent CDI (RCDI), although with limited success.[9] An alternative therapy that has been found to be both safe and effective in treating refractory CDI which is fecal microbiota transplantation (FMT). In allo-HSCT, systemic broad-spectrum antibiotics are frequently used for the treatment of infectious complications which make the gut more prone to dysbiosis and thereby making them more prevalent to suffer from CDI. This alteration likely accounts for rates of RCDI[9] of 10–20% after initial antibiotic treatment and recurrence rates as great as 40–65% in patients who have previously been treated for an RCDI episode.

FMT the new revolution!

FMT is a technique used to restore the normal body flora to the gut in cases of CDI. It involves instillation of the stool of a healthy donor through a nasogastric tube or colonoscopy into the gastrointestinal tract of the patient. More research is needed to determine the parameters of FMT use in patients with cancer.

How successful is it?

There was a significant change in gut microbial composition toward the donor microbiota and an overall increase in microbial diversity consistent with previous studies after FMT. FMT was successful in treating CDI using a diverse set of donors, and varying degrees of donor stool engraftment suggesting that donor type and degree of engraftment are not drivers of a successful FMT treatment of CDI. However, patients with underlying IBD experienced an increased number of CDI relapses (during a 24-month follow-up) and a decreased growth of new taxa, as compared to the subjects without IBD. Moreover, the need for IBD therapy did not change following FMT. These results underscore the importance of the existing gut microbial landscape as a decisive factor to successfully treat CDI and potentially for the improvement of the underlying pathophysiology in IBD.

To assess the efficacy, comparative[10] effectiveness, and harms of FMT for CDI, two randomized controlled trials (RCTs), 28 case series studies, and 5 case reports were done. Two RCTs and 21 case series studies (516 patients receiving FMT) reported using FMT for patients with RCDI. A high proportion of treated patients had symptom resolution; however, the role of previous antimicrobials is unclear. One RCT comparing FMT with two control groups (n = 43) reported resolution of symptoms in 81%, 31%, and 23% of the FMT, vancomycin, or vancomycin-plus-bowel lavage groups, respectively ($P < 0.001$ for both control groups vs. FMT). An RCT comparing FMT route (n = 20) reported no difference between groups (60% in the nasogastric tube group and 80% in the colonoscopy group; $P = 0.63$). Across all studies for RCDI, symptom resolution was seen in 85% of cases. In seven case series studies of patients with refractory CDI, symptom resolution ranged from 0% to 100%. Among seven patients treated with FMT for initial CDI, results were mixed.

RCDI is a consequence of intestinal dysbiosis and is particularly common following allo-HSCT.

FMT is an effective method of treating CDI by correcting intestinal dysbiosis by passive transfer of healthy donor microflora. FMT has not been widely used in immunocompromised patients, including allo-HSCT recipients, owing to concern for donor-derived infection. Here, we described initial results of an FMT program for CDI at a US allo-HSCT center. Seven allo-HSCT recipients underwent FMT between February 2015 and February 2016.[11] Mean time post allo-HSCT was 635 days (25–75 interquartile range [IQR] 38-791). Five of the patients (71.4%) were on immunosuppressive therapy at FMT; four had required long-term suppressive oral vancomycin therapy because of immediate recurrence after antibiotic cessation. Stool donors underwent comprehensive health and behavioral screening and laboratory testing of serum and stool for 32 potential pathogens. FMT was administered through the nasojejunal route in 6 of the 7 patients. Mean follow-up was 265 days (IQR 51-288). Minor post-FMT adverse effects included self-limited bloating and urgency. No serious adverse events were noted and all-cause mortality was 0%. Six of 7 (85.7%) patients had no recurrence; one patient recurred at day 156 post-FMT after taking an oral antibiotic and required repeat FMT, after which no recurrence has occurred. Diarrhea was improved in all patients and one patient with gastrointestinal GVHD was able to taper off systemic immunosuppression after FMT. With careful donor selection and laboratory screening, FMT appears to be a safe and effective therapy for CDI in allo-HSCT patients and may confer additional benefits. Larger studies are necessary to confirm safety and efficacy and explore other possible effects.

Issue of Mayo Clinic Proceedings, Patel *et al*.[12] presented their results on the use of FMT to treat RCDI using a standardized evaluation process and protocol. Over a 2-year period, 31 patients were treated. Three patients required more than one transplant procedure; in two of these patients, the second FMT was delivered through a nasojejunal feeding tube. Improvement or resolution of diarrhea occurred in 97% of the patients. The onset of improvement was rapid, with 26 of 30 patients (87%) experiencing improvement or resolution by 1 week. The response was durable in most patients, and six who had follow-up at 1 year reported maintained improvement. Adverse events occurred in one patient who experienced a self-limited colonic perforation during the colonoscopy.

Future of FMT

Over the past several years, FMT has been reported to be highly effective in treating patients with RCDI. However,

FMT has recently experienced a potential setback at most institutions since the US Food and Drug Administration (FDA) convened a public workshop on May 2–3, 2013, that addressed FMT, i.e. after acceptance of the article by Patel *et al*.[12] for publication in the proceedings is an unapproved new drug for which an investigational new drug (IND) application is required. For most institutions, obtaining an IND will be too cumbersome and time consuming. The FDA's decision is to put more restrictions on FMT due to certain unanswered questions among which the first and foremost is recipient safety.[13] As stated by the FDA, "the long-term effects of alterations in the gut microbiome are unknown."

The FDA now intends to "exercise enforcement discretion"[14] regarding IND requirements for the use of FMT to treat CDI unresponsive to standard therapies provided treating physicians obtain adequate informed patient consent or consent from a legally authorized representative. According to the FDA, "this informed consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks."[14]

Based on this, the use of FMT certainly appears to be in a fix. In the meantime, cautious use of FMT specifically for patients with RCDI not responsive to traditional antimicrobial therapy is advised.

Conclusions

FMT is the newest solution to RCDI patients suffering and not responding to the traditional antimicrobial regime. It should be noted that FMT carries the risk of infection transmission (human immunodeficiency virus, hepatitis, and retrovirus). Broad range of studies and trials is needed to be done before it can be used as a FDA approved treatment modality for RCDI.

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