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Intestinal aGVHD and infection after hematopoietic stem cell transplantation

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Background: We aimed to guide clinical nursing by studying the relationship between intestinal acute graft-versus-host disease and intestinal infection after hematopoietic stem cell transplantation.

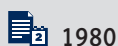
Material/Methods: We present an effective nursing method by comparing and analyzing the degree, duration time, and volume of diarrhea, and the distribution of pathogens in 44 patients who developed intestinal aGVHD after hematopoietic stem cell transplantation (24 patients with no intestinal infection).

Results: 21.4% of patients with grade I-II intestinal aGVHD developed into intestinal infection and 87.5% of patients with grade III-IV intestinal aGVHD developed into intestinal infection ($P < 0.05$). Higher mortality was found in the grade III-IV intestinal aGVHD patients with intestinal infection. Patient age had no effect on the incidence of GVHD according to our data ($P < 0.05$). We found remarkable differences in the amount and duration of diarrhea between patients with and without intestinal infection ($P < 0.05$). The most common pathogens cultivated were *Candida glabrata* (24%) and *Candida albicans* (22.67%).

Conclusions: The incidence of intestinal infection increased remarkably after intestinal aGVHD occurred. Severe aGVHD can easily lead to fungus infection. Nursing care can decrease the incidence of intestinal infection in aGVHD.

Key words: **hematopoietic stem cell transplantation • intestinal acute graft-versus-host disease • intestinal infection • nursing care**

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Background

Graft-versus-host disease (GVHD) remains one of the most frequent and severe complications of alloHSCT. Even when HLA-identical siblings are the source of HSC for infusion, the likelihood of developing clinically significant acute and chronic GVHD approaches 35% [1]. It is caused by immune reactions of donor T cells against disparate host histocompatibility antigens. Most GVH reactions are undesirable, and cause disease in skin, gut, and liver as the main target organs [2]. Acute graft-versus-host Disease (aGVHD) is the main complication following hematopoietic stem cell transplantation, and severe intestinal GVHD seriously affects the transplantation [3]. Therefore, it is essential to take proper and effective measures to reduce the incidence of intestinal complications. Each year, over 200 hematopoietic stem cell transplantation operations are performed in our hospital, which is the center for tumor therapy and bone marrow transplantation in this country. Here, we present the situation of intestinal aGVHD incidence and intestinal infection of the patients who had hematopoietic stem cell transplantation in our hospital. The relationship between intestinal aGVHD and intestinal infection after hematopoietic stem cell transplantation was analyzed. We emphasize the role of nursing care in preventing intestinal complications after hematopoietic stem cell transplantation.

Material and Methods

Clinical data

This study included 44 patients who developed intestinal aGVHD after hematopoietic stem cell transplantation operation in our hospital from January 2010 to December 2012; 20 cases developed intestinal infection and 24 cases did not. There were 27 male patients and 17 female patients. The average age was 31 years (31.41 ± 14.75 , range 17–54). The clinical disorders included acute myeloid leukemia (18 cases), acute lymphocytic leukemia (11 cases), myelodysplastic syndrome (5 cases), chronic myelocytic leukemia (5 cases), aplastic anemia (4 cases), and acute heterozygous cell leukemia (1 case). There were 21 cases treated with allogeneic hematopoietic stem cell transplantation, 11 cases treated with unrelated peripheral stem cell transplantation, 8 cases treated with related peripheral stem cell transplantation, 3 cases treated with autologous bone marrow transplantation, and 1 case treated with HLA haploidentical hematopoietic stem cell transplantation. Enteroscopy were performed in 12 patients. Significant intestinal mucosa hyperemia was found. Multiple erosion foci in red maculopapule were identified. Pathology biopsies showed the disappearance of intestinal mucosa villi and the desquamation of epithelial cells, as well as inflammatory necrosis. CMV inclusion bodies were not found.

Research method

A retrospective study was carried out based on the clinical data of the 44 aGVHD patients mentioned above. Patients' general data, the degree of diarrhea, duration, hospitalization days, and the pathogen distributions of patients with intestinal infection were surveyed and analyzed.

Intestinal aGVHD diagnosis and clinical grading

The diagnosis and clinical grading of aGVHD were performed according to the Seattle standard [4]. For patients with concomitant skin aGVHD or liver aGVHD (which usually occurred first), diagnosis was made if 1 or more of the following clinical manifestations were present: nausea, vomiting, anorexia, diarrhea, pain caused by abdominal spasm, abdominal distension, paralytic ileus, and intestinal bleeding. Gastrointestinal endoscopies were performed for patients who only had typical clinical manifestations of intestinal aGVHD. Biopsy tissues were used for pathology examinations to exclude other factors causing enteritis, especially CMV enteritis. According to the amount of diarrhea (AOD) of the patient per day, the severity of aGVHD was divided into 4 levels: I (AOD >500 ml/d), II (AOD >1000 ml/d), III (AOD >1500 ml/d), and IV (AOD >2000 ml/d, accompanied by abdominal pain, and/or intestinal obstruction).

The diagnostic criteria of intestinal infection

The diagnosis of intestinal infection was made according to the diagnostic criteria of hospital infection made by the Chinese Ministry of Health, the clinical manifestation of the patients, and the pathogenic bacteria detected in or cultivated from the excrement specimen.

Statistical treatment

All data were analyzed by t test using the SPSS13.0 software package. $P < 0.05$ meant the differences had statistical significance.

Results

Comparison of the diarrhea degree

Intestinal infection developed in 21.4% of patients with grade I–II aGVHD, and 87.5% of patients with grade III–IV aGVHD developed intestinal infection ($P < 0.05$, Table 1). Higher mortality was found in the grade III–IV aGVHD patients with intestinal infection (Table 2). Patient age had no effect on the incidence of aGVHD. The incidence of aGVHD on patients age 17–30 years vs. age 31–54 years were, respectively, 31.8% vs.

Table 1. The distribution of infection from GVHD (cases).

	Non-infection	Infection	
I-II	22	6	28
III-IV	2	14	16
Total	24	20	44

Table 2. The distribution of mortality of GVHD with and without infection.

	Non-infection	Infection	
I-II	0 (22)	0 (6)	28
III-IV	0 (2)	3 (14)	16
Total	24	20	44

Table 3. The patients' age had no effect on the incidence of aGVHD.

Ages	aGVHD (cases%)	
	Grade I-II (63.6%)	Grade III-IV (36.4%)
17-30 years	14 (31.8%)	7 (15.9%)
31-54 years	14 (31.8%)	9 (20.5%)
P-Value	P>0.05	P>0.05

31.8% in grade I-II aGVHD and 15.9% vs. 20.5% in grade III-IV aGVHD (P>0.05, Table 3).

Comparison of the amount of diarrhea, duration, and hospital days

Remarkable differences in the amount and duration of diarrhea between patients with and without intestinal infection were found (P<0.05), but the difference in hospital days showed no statistical significance (P>0.05, Table 4).

Table 4. Comparison of the duration time, volume of diarrhea and hospitalization days of the Intestinal aGVHD patients with or without intestinal infection $\bar{x}\pm S$.

	aGVHD patient without intestinal infection	aGVHD patient with intestinal infection	t	P
Hospitalization days (days)	35.5±12.96	33.67±7.53	0.30	0.771
Duration (days)	6.67±4.27	13.50±4.76	-2.615	0.026
Diarrhea amount (ml)	282.68±114.13	1433.33±559.81	-4.993	0.03

Table 5. The distribution and constituent ratio of the intestinal pathogenic bacteria (%).

Types	Number of cases	Constituent ratio (%)
<i>Candida glabrata</i>	18	24.00
<i>Candida albicans</i>	17	22.67
<i>Proteus mirabilis</i>	16	21.33
<i>Citrobacter freundii</i>	13	17.33
Enterotoxigenic <i>Escherichia coli</i>	3	4.00
<i>Citrobacter braakii</i>	3	4.00
<i>Candida krusei</i>	2	2.67
<i>Protens penneri</i>	1	1.33
<i>Edwardsiella tarda</i>	1	1.33
<i>Trichosporon inkin</i>	1	1.33
Total	75	100.00

The detection results of the pathogenic bacteria of patients with intestinal infection

Pathogenic bacteria were cultivated from the excrement specimens of 20 patients, making the intestinal infection rate 45.45%. Among the 75 pathogen strains cultivated, the 3 most common were *Candida glabrata* (18 strains, 24%), *Candida albicans* (17 strains, 22.67%), and *Proteus mirabilis* (16 strains, 21.33%) (Table 5).

Discussion

aGVHD is the main complication after allogeneic hematopoietic stem cell transplantation, and the incidence and mortality are very high. Increasing clinical studies have indicated that gastrointestinal damage plays a crucial role in the initiation and development of aGVHD. Due to the serious clinical

symptoms of gastrointestinal aGVHD, taking pertinent nursing measures in the early stage to prevent the complications is very important.

Pay attention to the degree of diarrhea

Patients with skin aGVHD usually develop gastrointestinal aGVHD several weeks later. However, gastrointestinal aGVHD can also arise without skin and hepatic involvement. The main clinical manifestation of patients with gastrointestinal aGVHD is the large amount of secretory diarrhea. The severity of diarrhea can be estimated by the patient's amount of diarrhea per day. Therefore, accurate evaluation of the amount and degree of diarrhea is of great importance. In this study, the diarrhea amount, degree, and duration were used to investigate the relationship between intestinal aGVHD in patients with and without intestinal infection. As shown in Tables 1 and 2, 21.4% (6/28) of patients with grade I–II intestinal aGVHD developed into intestinal infection and 87.5% (14/16) of patients with grade III–IV intestinal aGVHD developed into intestinal infection ($P<0.05$). Higher mortality (3/16) was found in the grade III–IV intestinal aGVHD patients with intestinal infection. Patients without intestinal infection mainly developed into I (66.67%) and II (25%) aGVHD, while patients with intestinal infection mainly developed into III (45%) and IV (25%) aGVHD. The study results indicate that the severity of diarrhea was closely related to intestinal infection. aGVHD patients with intestinal infection often have more severe symptoms than aGVHD patients without intestinal infection. A previous study showed that the mortality rate of III–IV aGVHD was above 50% [5]. Therefore, nurses must know the clinical features of aGVHD. Proper and effective treatment should be performed in the early stage to reduce the incidence of intestinal infection. AOD per day and duration are important factors. In this study, the difference in AOD and duration between aGVHD patients with and without intestinal infection was significant ($P<0.05$). Patients with intestinal infection usually had severe aGVHD. AOD per day and duration increased with aGVHD severity.

Pay attention to fungal infection

It has been documented that high incidence of invasive aspergillosis is associated with intestinal graft-versus-host disease following nonmyeloablative transplantation [6]. We cultivated pathogenic bacteria from the excrement specimens of 20 patients, making the intestinal infection rate 45.45%. The incidence of aGVHD tended to increase with the rate of intestinal infection. The pathogens detected or cultivated were mainly fungi, such as *Candida glabrata* and *Candida albicans*. Fungal opportunistic pathogens attack the human body when the immunity is low, causing opportunistic infection. Moreover, fungal infection can decrease immunity [7], thus aggravating the symptom of intestinal aGVHD. Because of chemotherapy and

long-term use of immunosuppressive agents and anti-bacterial agents, patients whose immune systems did not recover after stem cell transplantation were at high risk of fungal infection. It was reported by Yu that the risk of intestinal fungal infection increased after the use of broad-spectrum antibiotics [8] and could lead to dysbacteriosis by disturbing the normal intestinal flora. The rejection and damage of intestinal mucosa after stem cell transplantation often cause intestinal infection. Therefore, special attention must be paid to the high-risk population and the rational use of antibiotics to reduce intestinal infection. In addition, fecal culture must be performed in the early stage.

Pay attention to intestinal nursing

Perianal nursing

The patient's hemogram and digestive symptoms such as nausea, vomiting, diarrhea frequency and amount, abdominal spastic pain, abdominal distension, paralytic ileus, intestinal bleeding, and skin elasticity should be carefully observed. Accurate recording of the daily amount of stool was the key in the evaluation of aGVHD severity. Different nursing measures should be performed according to the severity of aGVHD. We showed that the diarrhea degrees of aGVHD patients with intestinal infection were mainly grade III–IV and indicated that the greater severity of aGVHD was associated with greater risk of intestinal infection. Therefore, close observation and intensive care of patients with severe aGVHD are needed. We found that 10 of 44 patients in this study had anal or perianal skin mucosal injury, including erosion, red swelling, and pain caused by frequent defecation. For these patients, bed rest was advised and forceful defecation should be avoided. After defecation, the perianal skin should be cleaned with a 1: 2000 chlorhexidine solution, then disinfected with iodophor. Sometimes, local exposure was advised to keep the skin dry. Local irradiation can be used when necessary to promote healing.

Dietary nursing

We prescribed liquid diet disinfected using a micro-wave oven for grade I and II aGVHD patients. In addition, special attention must be paid to the amount of food intake. Patients with grade III–IV aGVHD were prescribed fasting and water abstinence. Gastrointestinal decompression was introduced. At the same time, they were intravenously administered with 30% fat emulsion, compound amino acid, and 50% glucose injection. When the symptoms are alleviated after 1–2 weeks' treatment, liquid diet should be gradually resumed.

Protective isolation

When the peripheral leukocytes dropped to 1.0×10^9 after clinical treatment, the patient should be transferred to the laminar flow

ward to receive total environmental protection [9]. Strict aseptic procedures, disinfection, and isolation are necessary. It is essential to instruct the patient about self-care skills to protect the 5 sensory organs, skin, mucous membrane, urethral orifice, and anus. Cross-infection should be prevented by restricting visitors. Other protective measures included keeping the ward tidy, ultraviolet disinfection of indoor air twice a day for 30 minutes each time (once in the morning, once in evening), and wiping the tables and floor twice a day using chlorine-containing disinfectant.

Psychological nursing

Most patients with intestinal aGVHD were are great psychological pressure. We should try our best to comfort the patients and their family members, and to persuade them to face the disease calmly. In addition, it is necessary to feel compassion toward the patients and to allow for the bad temper of the patients caused by the illness. Chat with them at times and consider their demands. In the aspect of daily life nursing, we

should take each detail into consideration. For example, after collecting stool sample, drug application and disinfection should be performed in a timely fashion. Nurses should sponge off the patients and shampoo their hair twice a week. Every time after nursing, to remember say something such as "What else can I do for you?" or "I will see you again soon." These actions of positive psychological comforting and guidance play an indispensable role in the recovery of the patients.

Conclusions

Intestinal aGVHD and intestinal infection exacerbate the disease and increase the economic and psychological burden of the patients. Moreover, aGVHD is considered a major complication and cause of death after stem cell transplantation. Therefore, proper nursing care for such patients to prevent intestinal infection is very important and also has great social and economic benefits.

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