

Diarrhea in peripheral stem cell transplant recipients: a developing country's experience

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Abstract

Introduction: We aimed to determine the frequency and microbiological causes of diarrhea occurring during the first 100 days in allogeneic (allo-) and autologous (auto-) stem cell transplantation (SCT) patients.

Methodology: A total of 452 patients who underwent transplantation due to hematological or solid organ malignancy were included. From the administration of the conditioning regimen up to day 100 post-transplant, diarrhea cases lasting at least three days with a minimum of three episodes per day were evaluated.

Results: Cases of diarrhea were observed in 94 patients out of 227 subjects who received allo-SCT and in 107 patients out of 225 who received auto-SCT. The incidence rate of diarrhea in both patients undergoing autologous and allogeneic transplant was 47.5% and 41.4%, respectively. The cause of the diarrhea could be detected in 20.5% of auto-SCT patients and in 30.8% of allo-SCT patients. Parasitic infections were frequently observed in both autologous and allogeneic transplant patients in the first 20 days. In the late period, significantly more patients developed diarrhea in the allo-SCT recipient group than in the auto-SCT recipients due to graft versus host disease (GVHD) and cytomegalovirus (CMV) colitis.

Conclusions: This study revealed the causes of diarrhea and the prevalence and factors of parasitic infections in transplant patients in Turkey. All causative factors of diarrhea should be considered in detail, feces analyses should be evaluated for each patient, and endoscopic biopsy samples should be obtained when required in immunosuppressive patients undergoing stem cell transplantation.

Key words: diarrhea; stem cell transplantation; microbiological causes

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Introduction

Diarrhea is a frequently observed complication in the first three months following transplantation; it has the potential to deteriorate the general health status in stem cell transplantation (SCT) patients. It is hard to determine the exact etiology of the diarrhea in these patients. At the early period following SCT, bacterial and viral causes for diarrhea are more frequent; however non-infectious events such as conditioning regimens, medicines, and acute GVHD may also cause diarrhea [1]. Though the frequency of diarrhea in SCT patients is not known exactly, the incidence of transplant associated gastroenteritis has been reported

to be between 23% and 40% in the literature [1,2,3]. We aimed to determine the frequency of diarrhea in patients who underwent allogeneic and autologous SCT in the first 100 days following transplant, and to reveal the microbiological causes of the diarrhea.

Methodology

Patients

A total of 452 patients who underwent allo- or auto-SCT due to haematological or solid organ malignancy between January 2007 and February 2011 in Erciyes Stem Cell Transplantation Hospital were included in the study (225 auto-SCT, 227 allo-SCT).

The study was conducted through retrospective evaluation of patient hospital files and electronic records.

At the time of the SCT, each patient was treated in special single-patient rooms that had hepa filters. Diarrhea cases lasting at least three days with three or more episodes per day were evaluated from the administration of the conditioning regimen prior to transplantation up to day 100 following transplantation. The clinical approach used to assess patients with acute diarrhea is summarized in Figure 1. The following patient characteristics were examined: age, gender, underlying disease, type of transplant (auto-SCT or allo-SCT), presence of GVHD, fecal microscopy, fecal culture, fecal *Clostridium difficile* toxin, fecal CMV polymerase chain reaction (PCR), serum CMV PCR, and findings of the rectoscopic or colonoscopic biopsies.

Preventive and supportive treatment

All patients undergoing allo-SCT received oral fluoroquinolone prophylaxis (ciprofloxacin 1000 mg/day or moxifloxacin 400 mg/day) for the first 30 days for possible bacterial infections, oral valacyclovir prophylaxis (500 mg/day) for the first 30 days for herpes viruses, and oral fluconazole prophylaxis (400 mg/day) for the first 75 days for fungal infections. In addition, each patient also received oral metronidazole (1,500 mg/day) treatment for the first 30 days. For *Pneumocystis jiroveci* prophylaxis, oral trimethoprim/sulfamethoxazole (160 mg/day tablets, two days per week) was started prior to transplantation and continued up to day 180 after engraftment.

Before auto-SCT, patients were given oral fluoroquinolone prophylaxis (ciprofloxacin 1,000 mg/day or moxifloxacin 400 mg/day) for the first 30 days for bacterial infections, oral valacyclovir prophylaxis (500 mg/day) for the first 30 days for herpes viruses, and oral fluconazole prophylaxis (400

mg/day) for the first 30 days for fungal infections. All transplant patients received a low bacterial diet (LBD) from admission until discharge from the hospital. The LBD at the clinic omitted raw vegetables, salads, soft cheeses, raw meat products, most fresh fruits, tap water, and spices added after cooking. Furthermore, bread, cheese, and ham were individually packed and yogurt deserts, soda drinks, and soups were served in single-serving containers.

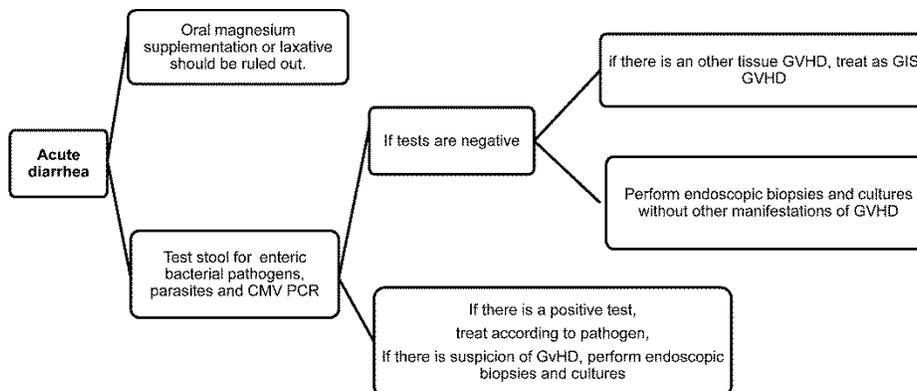
GVHD prophylaxis

In allo-SCT patients, methotrexate (15 mg/m² IV on day one, 10 mg/m² IV on days three and six), and cyclosporine (3 mg/kg/day IV) were used for acute GVHD prophylaxis. After transplantation, oral cyclosporine therapy at a dose of 5 mg/kg/day was maintained as a standard. In case of cyclosporine toxicity, treatment was switched to mycophenolate mofetil (2×1,000 mg/day oral) or mycophenolate sodium (2×720 mg/day oral). Diagnosis of GVHD was established through tissue biopsies in each clinically suspected patient. Liver biopsy for liver GVHD, rectoscopic or colonoscopic biopsy for gastrointestinal system (GIS) GVHD, and skin biopsy for dermal GVHD was taken. Diagnosis of acute GVHD was based on Glucksberg criteria accepted in 1999 [4] and in case of confirmed acute GVHD, 2 mg/kg/day methylprednisolone was started as an add-on treatment.

Microbiological methods

Patients’ fecal specimens were assessed in the microbiology laboratory. The laboratory examined CMV DNA by real-time PCR. The MagNaPure instrument was used to extract viral DNA from plasma. Real-time PCR was conducted using the Light Cycler CMV Quant kit (Roche Diagnostics, Mannheim, Germany) following the manufacturer’s instructions. The stool samples (approximately 1.5 g) were freshly

Figure 1. Clinical approach for patients profiling



collected and immediately placed and homogenized in a conical tube containing 5 mL of STAR buffer (Stool Transport and Recovery buffer, Roche Diagnostics, Mannheim, Germany); chloroform (500 μ L) was added and the sample was centrifuged for one minute at 3,300 rpm. Total nucleic acids (TNA) were isolated from the supernatant using MagNA Pure LC (Roche Diagnostics, Mannheim, Germany). Dynamic range for real-time PCR was 7×10^2 – 5.6×10^8 copies/mL, with an analytic sensitivity of < 235 copies/mL. No amplification results were reported as < 235 copies/mL. The low positive (< 700 copies/mL) definition was used for results between 235 and 700 copies/mL.

The presence of *C. difficile* toxin A and/or toxin B was determined using the immunochromatography method (Mascia Brunelli, Milano, Italy). For fecal cultures, samples were transported in Cary-Blair medium and inoculated onto blood agar or hektoen enteric agar (Difco, Detroit, USA). For *Campylobacter* species, modified charcoal cefoperazone deoxycholate agar (Oxoid, Basingstoke, UK) was examined after 48-72 hours of incubation at 42°C in a microaerophilic medium in an anaerobic jar (Oxoid, Basingstoke, UK) using a Campy-Gen kit (Oxoid, Basingstoke, UK). Isolates suspected of being *Salmonella* or *Shigella* spp. were identified by the Kauffmann–White scheme using conventional biochemical methods. Serological typing was performed by slide agglutination method using antisera (Difco, Detroit, USA). For the parasites, fresh stool samples were first analyzed by light microscopy for the detection of helminthes and protozoa using native Lugol. The modified acid-fast staining was used to detect *Cryptosporidium* spp.

Enterocytozoon bieneusi and *Encephalitozoon intestinalis* antigens were detected by the immunofluorescent antibody test using monoclonal antibodies anti-microsporidia (Bordier Affinity Products SA, Crissier, Switzerland). Briefly, stool samples were diluted with phosphate buffered saline (PBS) and filtrated through a 50 μ m filter for diagnosis of immunofluorescence. Two μ L of the fecal sample suspension was put on 18-well slides and dried for one hour. The slides were fixed with methanol and dipped subsequently in acetone for 10 minutes at -20°C . Twenty μ L of the monoclonal antibodies was added to each slide and incubated for 30 minutes at room temperature in a humid atmosphere. The slides were washed with PBS three times. Twenty μ L of conjugate was added to each slide and incubated for 30 minutes at room temperature in the dark. A coverslip was mounted on each glass slide with three drops of anti-

fading fluorescence mounting medium and viewed with a fluorescence microscope.

Demographic characteristics of patients

Table 1 gives the demographic characteristics of patients.

Conditioning regimens

Table 2 gives the conditioning regimens used for patients prior to transplantation.

Results

Diarrheal episodes of 201 patients were examined. The median day of diarrhea onset was day -2 for the period preceding transplantation, and day 5 for the period starting with transplantation and thereafter. The median day of diarrhea onset was day 5.5 in allo-SCT patients and day 4 in auto-SCT patients. Diarrhea was observed in 18 patients preceding transplantation. Twenty-six patients had more than one episode. Table 3 gives the time of diarrhea onset.

Cases of diarrhea lasting at least three days with three or more episodes per day were observed in 94 of 227 patients who received allo-SCT and in 107 of 225 patients who received auto-SCT. The cause of the diarrhea was detected in 20.5% of the auto-SCT patients and in 30.8% of the allo-SCT patients.

Serum CMV PCR positivity was detected in 66 patients with allo-SCT and in 50 patients with auto-SCT during diarrheal episodes. Of patients with positive serum CMV PCR results, 41 had low positivity (25 auto-SCT patients, 16 allo-SCT patients). Twelve patients with serum CMV PCR positivity were also positive for fecal CMV PCR (three auto-SCT patients, nine allo-SCT patients). *Cryptosporidium parvum* was detected in the rectoscopic biopsy material and in a feces sample of one allo-SCT patient. One patient grew *Salmonella* spp. identified as *Salmonella* group C. The *C. difficile* toxin was detected in seven patients. Table 4 shows all of the causes detected in patients with diarrhea by number of days.

GIS GVHD was detected in 15 patients with diarrhea. No parasites or bacteria were detected in any of these patients, and 6 patients were positive by CMV PCR. All patients with isolated GIS GVHD were biopsied through rectoscopy or colonoscopy, and diagnosis was confirmed histopathologically. Of the 201 patients, 1 auto-SCT patient and 22 allo-SCT patients underwent rectoscopy. Table 5 gives the GVHD sites and number of patients.

Table 1. Demographic characteristics of patients

	Auto-SCT	Allo-SCT
Patients, n (%)	107 (53.2 %)	94 (46.8%)
Age (years, average)	44.4	34.8
Gender (F/M)	31/76	39/55
Underlying disease		
Acute myeloid leukemia (AML)	6	45
Acute lymphoblastic leukemia (ALL)	-	28
Multiple myeloma (MM)	40	1
Non Hodgkin's lymphoma	36	-
Hodgkin's lymphoma	19	2
Others	6	18

Others include chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), aplastic anaemia (AA), myelodysplastic syndrome (MDS), myelofibrosis, (NHL), paroxysmal nocturnal hemoglobinuria (PNH), fanconi aplastic nemia (FAA), biphenotypic leukemia, solid tumours

Table 2. Conditioning regimens

Conditioning regimen (number of patients)	Auto-SCT	Allo-SCT
Cyclophosphamide/TBI	-	29
Cyclophosphamide/Busulfan	6	48
BEAM	55	-
Melphalan	40	-
Others	6	17

TBI: total body irradiation; BEAM: BCNU, Etoposide, ARA-C, Melphalan;

Others: fludarabine/cyclophosphamide, fludarabine/busulfan/antitimosit globuline

Table 3. Time of diarrhea onset

Day of onset of diarrhoea	Episode number of diarrhea	
	Auto-SCT, n = 115 (%)	Allo-SCT, n = 109 (%)
Pre-transplant	2 (1.7)	16 (14.7)
Day 0-20	105 (91.3)	67 (61.5)
Day 20-100	8 (7)	26 (23.8)

Table 4. Causes of diarrhea according to days

	Auto-SCT, n = 115 (%)	Allo-SCT, n = 109 (%)
Pre-transplant	Unknown etiology 2 (1.73)	Unknown of etiology 16 (14.67)
Day 0-20	Blastocystis hominis 7 (6.08) Giardia intestinalis 4 (3.47) Blastocystis hominis + Entamoeba hartmani + Entamoeba coli 1 (0.86) Enterocytozoon bienewisi + Encephalitozoon intestinalis 1 (0.86) Giardia intestinalis + Blastocystis hominis 1 (0.86) Hymenolepis nana + Blastocystis hominis 1 (0.86) Clostridium difficile 4 (3.47) Undetected of etiology 86 (74.78)	Cryptosporidium parvum 1 (0.91) Encephalitozoon intestinalis 2 (1.83) Enterocytozoon bienewisi + Encephalitozoon intestinalis 1 (0.91) Giardia intestinalis 1 (0.91) Group c Salmonella 1 (0.91) Clostridium difficile 3 (2.75) Undetected of etiology 58 (53.21)
Day 20-100	CMV colitis 3 (2.60) Undetected etiology 5 (4.34)	Blastocystis hominis 1 (0.91) Entamoeba spp. A 1 (0.91) CMVcolitis 3 (2.75) CMVcolitis + GVHD 6 (5.50) GVHD 15 (13.76)

Table 5. GVHD sites and number of patients

GVHD sites	Number of patients
GIS	6
Liver and GIS	7
Liver, skin, and GIS	2

Discussion

Stem cell transplantation puts patients at high risk for bacterial, fungal, and viral infections, and diarrhea is a frequently observed complication during the first three months following transplantation. The condition is often troublesome and has a wide range of differential clinical diagnoses [5]. In our study, 201 of 452 SCT recipients (44%) experienced one or more episodes of diarrhea from the first day of the conditioning regimen to day 100 following transplantation. The incidence rate of diarrhea in both patients undergoing autologous and allogeneic transplant was high (47.5% and 41.4%, respectively). In the pre-transplant period, a cause of infectious diarrhea could not be determined in all diarrhea patients. Since most of the episodes were observed during days 0–20 post-transplant in allo- and auto-SCT patients, these episodes were probably caused by infections related to severe leukopenia, the GI mucosa damaging effect of the conditioning regimen, and the use of a large quantity of many medications. More patients developed diarrhea in the allo-SCT recipient group than in the auto-SCT recipients (23.8% vs. 7%) in the late period after day 20. This difference seems to be associated with GVHD. These results are similar to results found in other studies in the literature [1].

Parasitic infections were more frequently observed in autologous transplant patients than in allogeneic transplant patients during the first 20 days. *Blastocystis* species have been widely observed all over the world, though their prevalence differs between countries. It is a matter of debate in the literature as to whether *Blastocystis* is a cause of disease [6]. Some studies have suggested that it can be accepted as a cause of disease or parasitic infection in immunocompromised patients [7,8]. In our study, this pathogen was found to be the only cause of diarrhea in eight patients, though in three patients, it was found together with other pathogens.

E. bienersi and *E. intestinalis* are reported here for the first time in patients with diarrhea who had undergone hematopoietic SCT, although these microsporidia have been shown to be etiological agents of diarrhea in other immunocompetent or immunocompromised conditions [9-12]. We found *E. intestinalis* in two patients, and both *E. bienersi* and *E. intestinalis* in two patients. Since these pathogens cause infrequent infections among transplant recipients, they are rarely taken into account during the differential diagnosis of infections in this population.

Giardia intestinalis, which is a commonly encountered cause of diarrhea in the SCT community, was more frequently observed in the auto-SCT than in the allo-SCT group. The lower frequency in allo-SCT patients was considered to be due to the administration of metronidazole prophylaxis during the first month post-transplant.

Twelve patients considered to have CMV colitis had both clinical features and fecal CMV PCR positivity (three auto-SCT patients, nine allo-SCT patients). Cytomegalovirus infection is among the prominent causes of morbidity in allo-SCT patients. Serologic status of the donor and recipient, GVHD, steroid therapy, and T-cell depletion are accepted as major risk factors for CMV infection [13,14,15-24]. Administration of prophylactic or pre-emptive therapy against CMV has been successful in reducing the incidence of CMV infection. Nevertheless, breakthrough CMV infection and gastrointestinal CMV disease in particular remain among the most important infectious complications [25].

In our study, GIS GVHD was detected in 7.4% of patients with diarrhea. None of their tests for parasites and pathogenic bacteria were positive; however, six patients were positive for fecal CMV PCR. The cause for diarrhea in these six patients was considered to be GVHD together with CMV colitis. Concomitant antiviral and immunosuppressive therapy was administered to the patients. Given the high incidence of GIS GVHD, its increase in morbidity and mortality, and its responsiveness to immunosuppressive therapy with steroid-based regimens, this condition is a primary concern as a cause of diarrhea in allo-transplant patients [5].

We detected the *C. difficile* toxin in 3.4% of our patients. The incidence of *C. difficile* associated with diarrhea in auto-SCT recipient patients has been reported to be between 5% and 7% [26,27,28]. This pathogen is the leading cause of infectious diarrhea in hospitalized patients and is a chief concern for patients undergoing SCT. The overall one-year incidence of *C. difficile* infection (CDI) was reported to be 9.2% in SCT recipient patients. Risk factors and the natural history of CDI are not fully established in SCT patients, but in allo-SCT patients are thought to be chemotherapy administration before conditioning for SCT, broad-spectrum antibiotics, and acute GVHD. A strong relationship has been reported between early CDI and subsequent development of GIS GVHD in the year following allo-SCT. GIS GVHD also increases the risk for recurrent CDI [29]. In our study, diarrheal episodes of all patients with the *C. difficile*

toxin occurred within the first 20 days following transplant, and two patients also developed GIS GVHD.

Among the allo-SCT recipients, *C. parvum* infection was detected in one patient. In this patient, diarrhea started in the first 20 days following transplant, *C. parvum* was detected in rectoscopic biopsy material and feces, and the systemic disease developed with elevation of hepatic enzymes during follow-up (results not shown). Cryptosporidiosis is associated with diarrhea, and the agent is carried asymptomatically in the intestines [30,31]. Intestinal infection might be associated with the activation of latent *Cryptosporidium* infection [32]. In a prospective study, *Cryptosporidium* was found in feces as the diarrheal agent in 14% of the hematologic malignancy patients with diarrhea, and 1.4% of the patients were found to be asymptomatic [33]. However, the authors reported that although *Cryptosporidium* infection is not frequent in SCT patients [3,34], it might be severe enough to cause systemic disease when present.

Viruses are very common pathogens causing gastroenteritis after SCT. Adenovirus, norovirus, and rotavirus have been frequently reported [35-37]. The incidence of viral gastroenteritis is reported to be approximately 20% in autologous and allogeneic SCT patients [36]. Unfortunately, detection of viruses is not performed in our center. Viral pathogens should be considered, especially if the others reasons are excluded.

While the causes of the diarrhea episodes were found in 29.8% of the patients, a cause could not be detected in the remaining patients. This could be due to the use of prophylactic oral fluoroquinolone, which impedes the observation of *Salmonella*, *Campylobacter*, and other toxin-producing bacteria, and to pre-emptive antiviral therapy in patients found to be serum positive for CMV, which prevents CMV infection.

This study was conducted to determine the microbiological causes of diarrhea in our center. Our results could be generalized to the causes of diarrhea and, in particular, the prevalence and the factors of parasitic infections in transplant patients in developing countries. We conclude that all causative factors of diarrhea should be considered in detail, feces analyses should be evaluated for every SCT patient, and endoscopic biopsy samples should be obtained when required in immunosuppressive patients undergoing SCT. Agents that do not normally cause infection in healthy individuals may cause atypical conditions in immunosuppressive transplant patients. Therefore,

even very rarely encountered microorganisms should also be considered, and care should be exercised in differential diagnosis.

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