Biol Blood Marrow Transplant 21 (2015) 159–164

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Incidence, Risk Factors, and Outcome of Cytomegalovirus Viremia and Gastroenteritis in Patients with Gastrointestinal Graft-versus-Host Disease

Divaya Bhutani [1,*], Gregory Dyson [1,2], Richard Manasa [1], Abhinav Deol [1], Voravit Ratanatharathorn [1], Lois Ayash [1], Muneer Abidi [1], Lawrence G. Lum [1], Zaid Al-Kadhimi [3], Joseph P. Uberti [1]

[1] *Karmanos Cancer Institute, Wayne State University, Detroit, Michigan*
[2] *Department of Oncology, Wayne State University, Detroit, Michigan*
[3] *Winship Cancer Institute, Emory University, Atlanta, Georgia*

Article history:
Received 16 July 2014
Accepted 6 October 2014

Key Words:
Allogeneic stem cell transplantation
Graft-versus-host disease
Cytomegalovirus viremia
Cytomegalovirus gastroenteritis

A B S T R A C T

Gastrointestinal (GI) graft-versus-host disease (GVHD) is one of the most common causes of morbidity and mortality after allogeneic stem cell transplantation. In addition, cytomegalovirus (CMV) infection of the gastrointestinal tract can complicate the post-transplantation course of these patients and it can be difficult to differentiate the 2 diagnoses given that they can present with similar symptoms. We retrospectively analyzed 252 patients who were diagnosed with GI GVHD to evaluate the incidence, risk factors, and outcomes of CMV viremia and CMV gastroenteritis in these patients. The median age at the time of transplantation was 51 years, 35% were related donor transplantations, and 65% were unrelated donor transplantations. A total of 114 (45%) patients developed CMV viremia at a median of 34 days (range, 14 to 236 days) after transplantation. Only recipient CMV IgG serostatus was significantly associated with development of CMV viremia ($P < .001$). The incidence of CMV viremia with relation to donor (D) and recipient (R) CMV serostatus subgroups was as follows: D+/R+, 73%; D−/R+, 67%; D+/R−, 19%; and D−/R−, 0. A total of 31 patients were diagnosed with a biopsy-proven CMV gastroenteritis; 2 patients had evidence of CMV gastroenteritis and GVHD on the first biopsy and 29 on the second biopsy. Median time to development of CMV gastroenteritis was 52 days (range, 19 to 236 days) after transplantation. Using death as a competing risk, the cumulative incidence of CMV gastroenteritis at 1 year was 16.4%. The incidence of CMV gastroenteritis in relation to the donor/recipient serostatus was as follows: D+/R+, 22%; D−/R+, 31%; D+/R−, 12%; and D−/R−, 0. Median follow-up time for the 252 patients was 35.4 (95% CI 23.8 to 44.8) months. The estimated overall survival rate at 1 and 2 years was .45 (95% confidence interval [CI], .39 to .52) and .39 (95% CI, .33 to .46), respectively. Of the examined variables, those related to the overall survival were maximal clinical GVHD grade ($P < .001$) and development of CMV gastroenteritis ($P = .008$). Development of CMV viremia was not associated with increased mortality. In conclusion, CMV gastroenteritis is common complication in patients with GI GVHD and can adversely affect the prognosis.

INTRODUCTION

Cytomegalovirus (CMV) infection and disease remain a major cause of morbidity and mortality after allogeneic and unrelated stem cell transplantation [1-5]. Ganciclovir was introduced in the late 1980s and is used for both treatment and prevention of CMV disease [6,7]; however, despite improvement in treatment, CMV continues to be a major problem in patients after allogeneic stem cell transplantation (allo-SCT). One major challenge in the management of these patients is the differentiation between gastrointestinal (GI) graft-versus-host disease (GVHD) and CMV gastroenteritis. These 2 diseases have overlapping symptoms and signs, which makes treatment decisions difficult without biopsy confirmation. In addition, the use of CMV viremia to guide treatment may often be misleading. Use of a preemptive approach (initiation of ganciclovir therapy based on

Financial disclosure: See Acknowledgments on page 164.

* Correspondence and reprint requests: Divaya Bhutani, MD, Department of Bone Marrow Transplantation, Karmanos Cancer Institute, 4100 John R, 4 HWCRC, Rm: 4247, Detroit, MI 48201.
E-mail address: bhutanid@karmanos.org (D. Bhutani).

http://dx.doi.org/10.1016/j.bbmt.2014.10.004
1083-8791/

detection of CMV viremia) is currently the strategy used by most centers as a method to prevent CMV organ disease. But there are instances in which the CMV organ disease can develop without preceding CMV viremia. In a study of 14 patients with biopsy-proven CMV gastroenteritis, only 50% had a positive CMV quantitative PCR (qPCR) before development of the CMV colitis [8]. Thus, making the diagnosis of CMV gastroenteritis in patients with pre-existing GVHD and worsening symptoms is difficult.

The purpose of our study was to assess the incidence, risk factors, and prognosis of patients who develop CMV viremia and CMV gastroenteritis after being diagnosed with GI GVHD. We also studied the effectiveness of using the CMV qPCR as a guide to preemptive treatment in these patients and evaluated the efficacy of repeat gut biopsies for diagnosis of CMV gastroenteritis in patients with prior biopsy-proven GI GVHD.

MATERIALS AND METHODS

The Wayne State University institutional review board approved this study. We retrospectively reviewed charts of patients who underwent allo-SCT at our institution from January 2005 to December 2011. The eligibility criteria included development of signs or symptoms of acute or chronic GI GVHD at any time after transplantation. These included development of otherwise unexplained nausea, vomiting, anorexia, abdominal pain or cramps, diarrhea, failure to thrive, and weight loss [9,10]. Grade of GVHD was determined clinically based on established criteria [9,10]. Variables assessed for risk factors of the development of CMV viremia and CMV gastroenteritis were age, gender, race, number of transplantations, donor (related or unrelated), HLA mismatch, graft source (peripheral blood or bone marrow), recipient/donor CMV IgG serostatus, underlying diagnosis, disease status at the time of transplantation, conditioning regimen, GVHD prophylaxis regimen, thymoglobulin use, acute GVHD grade and peak CMV qPCR.

CMV Monitoring

All patients were monitored for development of CMV viremia by either CMV pp65 antigenemia or CMV qPCR on a regular intervals (duration varied between every 1 to 2 weeks, depending on the clinical situation and frequency of clinic visits) for the duration of post-transplantation immunosuppression. Between January and December of 2005, we monitored the CMV viremia using pp65 antigenemia using direct fluorescence antibody test. Out of the 252 patients, 33 had monitoring done by the CMV Pp65 antigenemia and the rest were monitored by the CMV PCR. Thereafter, CMV qPCR was employed as our method of CMV monitoring. CMV viremia was present if there were greater than 250 copies/mL of CMV DNA. Any patient with a CMV qPCR of greater than 1000 copies/mL was started on therapy with i.v. ganciclovir. Patients with 250 to 999 copies/mL were followed twice weekly and treatment was initiated if there was a consistent rise of CMV viremia. Ganciclovir 5 mg/kg intravenous piggyback twice a day was given as therapy until the CMV qPCR turned negative or at least for 2 weeks if no significant hematologic toxicity was encountered.

GI Biopsies

We attempted to perform routine upper and lower GI biopsies in any patient suspected of having GI GVHD. Patient without CMV viremia were not treated with ganciclovir unless there were histologic documentation of GI involvement. The decision to do a second GI biopsy in patients with a prior diagnosis of GI GVHD was based on persistent or worsening of GI symptoms during or after adequate treatment of GVHD.

Outcomes

Primary event of interest was the development of biopsy-proven CMV gastroenteritis after the initial diagnosis of GI GVHD. The biopsy diagnosis was based on immuno-histochemistry on the gut tissue for CMV. The secondary events of interest were development of CMV viremia, which was defined by positivity of either CMV pp65 antigenemia or CMV qPCR at any time after the allogeneic stem cell transplantation and overall survival, defined as death from any cause after allogeneic stem cell transplantation.

Statistical Analysis

Given that death was a competing event for the other 2 outcomes, we used a competing risks regression model for the CMV viremia and CMV gastroenteritis outcomes. Standard Cox regression method was used for the overall survival outcome.

The following algorithm was used to construct the survival phenotype for both CMV viremia and CMV gastroenteritis outcomes: first, for patients with CMV viremia, the date of first day of CMV viremia detected by qPCR or antigenemia was used as the event date. For the overall survival phenotype, the date of death was used as the event date for those patients who died. For those patients who neither had CMV viremia or a death event, the date that CMV viremia was last measured was used as the censoring date. For the CMV gastroenteritis outcome, the censoring date was the date of the last biopsy that was negative for CMV gastroenteritis.

RESULTS

Patient Characteristics

Between January 2005 to December 2011, 252 of 780 patients who underwent allo-SCT at our institution had a clinical diagnosis of GI GVHD, confirmed by histology in 94%. Three groups were identified: GI GVHD only, GI GVHD with CMV viremia, and GI GVHD with CMV viremia and CMV gastroenteritis. The 3 groups were compared for various characteristics, as shown in Table 1. There were 9 patients for which there was no biopsy performed who are still included in Table 1. They were excluded for analysis of CMV gastroenteritis.

The median age of the patients was 51 years (range, 20 to 70 years) with an equal distribution of males to females (131 of 121). A matched sibling donor was used for 89 of 252 (35%) of the patients and a matched unrelated donor was used in 163 of 252 (65%). Degree of HLA mismatch was 10/10 in 163 of 252 (64%), 9/10 in 57 of 252 (23%), and 8/10 in 29 of 252 (11.5%) patients. Peripheral blood stem cells were used for transplantation in the majority of patients (238 of 252), bone marrow harvest was used in 12 patients, and cord blood was used in 2 patients. A full-intensity conditioning regimen was used in 178 of 252 (71%) of patients and a reduced-intensity conditioning regimen was used in 74 of 252 (29%) of patients. CMV IgG serostatus of donor (D) and recipient (R) was as follows: D+/R+, 78 of 252 (31%); D−/R+, 67 of 252 (27%); D+/R−, 33 of 252 (13%); and D−/R−, 74 of 252 (29%) (Table 1). The patient characteristics and demographics were evenly distributed across 3 groups, with the exception of CMV serostatus and race (Table 1).

GI GVHD Characteristics

The median time to development of GI GVHD was 27 days (range, 5 to 238 days). Fifteen patients were diagnosed with hyperacute GVHD starting within 14 days (range, 5 to 14 days) of transplantation. The majority of patients 248 (98%) developed GI GVHD before day 100 after transplantation. Four patients developed GI GVHD after day 100 after transplantation; 2 of these 4 patients had their immunosuppression discontinued because of disease relapse. The maximal overall clinical grade of II, III, and IV GVHD was seen in 37%, 33%, and 30% of patients, respectively. The median time from stem cell transplantation to first GI biopsy was 33 days (range, 12 to 292 days). Histological confirmation of GI GVHD was confirmed by a biopsy in 239 of 252 (94%) of patients. Of the 13 patients who did not have histologic confirmation of GVHD, 9 patients were clinically unstable to undergo biopsy and 4 patients had normal histology but were felt to have clinical GI GVHD. Among the patients with a positive biopsy, the histologic grade of GVHD was grade I, II, III, and IV in 11%, 27%, 22%, and 40% of patients, respectively. The degree of correlation between the clinical and histologic grade of GVHD was moderate, with a Kendall's tau correlation of .48. Systemic steroids were used in 96% of patients for