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Regimen-Related Mucosal Injury of the Gut Increased the Incidence of CMV Disease after Allogeneic Bone Marrow Transplantation

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Cytomegalovirus (CMV) infection is 1 of the major causes of morbidity in patients undergoing allogeneic stem cell transplantation (allo-SCT). The incidences of CMV antigenemia and CMV disease in 43 patients who received allogeneic bone marrow transplantation (BMT) using a reduced-intensity conditioning (RIC) regimen, which mainly consisted of fludarabine (Flu), busulfan (Bu), and total body irradiation (TBI), were compared with those in 68 patients who received a myeloablative conditioning (MAC) regimen, and risk factors for CMV antigenemia and CMV disease were identified. Before engraftment, grade 3-4 mucosal injury because of the conditioning regimen was significantly decreased in RIC patients (stomatitis: $P = .02$; diarrhea: $P < .01$). Rate of engraftment, incidences of acute graft-versus-host disease (aGVHD), and rate of corticosteroid administration were not different in RIC patients and MAC patients. Although the incidences of CMV antigenemia were not significantly different in RIC patients and MAC patients (64.1% versus 57.8%, log rank, $P = .59$), the incidence of CMV disease was significantly decreased in RIC patients (5.4% versus 20.3%, log rank, $P = .04$). CMV seropositivity in the patients ($P < .01$) and corticosteroid administration ($P < .01$) were revealed by multivariate analysis to be significant risk factors for CMV antigenemia. Grade II-IV aGVHD ($P = .02$) and grade 3-4 diarrhea before engraftment ($P = .04$) were revealed to be risk factors for CMV disease. The present study is the first study to show that severe diarrhea before engraftment is a significant risk factor for CMV disease. In summary, risk of CMV disease was significantly decreased in patients without severe mucosal injury of the gut because of the conditioning regimen before engraftment.

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INTRODUCTION

Cytomegalovirus (CMV) infection is 1 of the major causes of morbidity in patients undergoing allogeneic stem cell transplantation (allo-SCT). Preemptive antiviral therapy has been shown to reduce the risk of CMV disease [1-3]. Major risk factors for CMV infection are serologic status of the donor and recipient, graft-versus-host disease (GVHD), corticosteroid administration, and T cell depletion [1,2,4-13]. Recently, reduced-intensity conditioning (RIC) regimens have been developed for patients who had been considered ineligible for SCT using a myeloablative conditioning (MAC) regimen because of advanced age or medical contraindications [14,15]. Although many studies have shown that infection before engraftment was reduced in patients undergoing RIC because of a shorter neutropenic period and less severe mucositis [16-19], risks of CMV infection have not been substantially reduced after RIC-SCT [1,7,8,10-12]. Again, we need to consider the difference in CMV infection depending on the RIC regimen because various RIC protocols have been developed and the toxicity profile might vary from 1 protocol to another because of variability in the degree of

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immunosuppression or myeloablation [8,10,11,14,15]. We should also consider the difference in CMV infection depending on the stem cell source [8,20].

The present study was a retrospective analysis to compare the incidence of CMV infection in 43 consecutive patients who received bone marrow transplantation (BMT) using an RIC regimen, which mainly consisted of fludarabine (Flu), busulfan (Bu), and total body irradiation (TBI) (Flu/Bu/TBI) in our institution with that in 68 patients who received MAC-BMT during the same period. The risk factors for CMV antigenemia and development of CMV disease were also investigated.

PATIENTS AND METHODS

Patients

One hundred eleven consecutive adult patients with advanced hematologic diseases who received allogeneic BMT using RIC regimens (43 patients) or MAC regimens (68 patients), between September 2000 and March 2007, at Hokkaido University Hospital were analyzed for CMV infections. Twenty-eight patients received an RIC regimen because of advanced age (>50 years), and 10 received an RIC regimen because of prior autologous transplantation (5 patients overlapped with the patients of advanced age). A difference in the risk of CMV infection depending on stem cell source has been reported [8,20], and we cannot use peripheral blood stem cells (PBSC) from an unrelated donor (PBSC can be used only from related donors) in Japan. Moreover, it has been reported that cord blood showed differences in the incidences of infections and kinetics of immunologic recovery from other stem cell sources. Therefore, we analyzed only patients who received BMT. Patients who had already received allogeneic SCT were excluded from this study.

Conditioning Regimens

In the RIC group, 38 (88.4%) of the patients received a conditioning regimen of Flu/Bu/TBI, which consisted of Flu at a dose of 30 mg/m^2 once daily administered intravenously (i.v.) on days −7 to −2 (total dose: 180 mg/m^2) and Bu at 1 mg/kg 4 times daily administered orally (p.o.) on days −3 and −2 (total dose: 8 mg/kg) combined with fractionated TBI at 2 Gy twice daily on day −1 (total dose: 4 Gy), and the other 5 patients received Flu plus melphalan (mel; n = 4) or Flu plus cyclophosphamide (Cy) (n = 1). In the MAC group, 10 patients (14.7%) received a conditioning regimen of Cy/TBI, which consisted of Cy at a dose of 60 mg/kg once daily administered i.v. on days −5 and −4 combined with fractionated TBI at 2 Gy twice daily on days −3 to −1 (total dose: 12 Gy), and 44 patients (64.7%) received Cy/TBI plus VP-16 (VP/Cy/TBI), in which VP-16 was added to Cy/TBI at a dose of 15 mg/kg once daily administered i.v. on days −7 and −6 (total dose: 30 mg/kg) [21,22]. The other patients received other regimens of Bu/Cy or Cy/TBI plus cytarabine. GVHD prophylaxis consisted of cyclosporine A (CsA) and a short course of methotrexate (MTX; 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) for HLA-matched related donor recipients, and tacrolimus plus a short course of MTX was given for HLA-matched unrelated donor or HLA-mismatched donor (MMD) recipients. The patients received GVHD prophylaxis from day −1 for 3 months, and drug doses were tapered in patients with no active GVHD, the dose of CsA or tacrolimus being adjusted by plasma level.

Supportive Care and Infection Prophylaxis

Levofloxacin (300 mg daily) was administered p.o. for prevention of bacterial infections until engraftment, and antifungals (fluconazole at 400 mg daily p.o., itraconazol capsules at 200 mg daily p.o., or micafungin at 100 mg daily i.v.) were administered for prevention of fungal infections. Oral acyclovir was given on day −7 to day 35 for prevention of herpes simplex virus (HSV) infection. Oral trimethoprim-sulfamethoxazole or pentamidine inhalation was started after engraftment for prevention of Pneumocystis jiroveci infection. Prophylactic intravenous immunoglobulin (10 g) was given biweekly until serum IgG levels reached >400 mg/dL. Prednisolone was administered for patients who developed grade ≥ii acute GVHD (aGVHD) at a dose of 0.5-1.0 mg/kg daily according to a physician's decision. The dose of prednisolone administered was lower than the dose used in other countries because of the lower incidence of critical aGVHD in Japan [23].

CMV Surveillance and Treatment

Pretransplant serum samples from all patients and donors were tested for serologic evidence of past infection with CMV by an enzyme-linked immunosorbent assay or complement fixation test. When a patient and a donor were both negative for CMV, patients received CMV-negative blood products. When a patient or a donor was positive for CMV, the patient was given unscreened blood products. Surveillance blood CMV pp65 antigenemia was monitored once or twice a week between engraftment and day 100 post-SCT [1,10,24]. Patients with persistent CMV infection, GVHD, and/or corticosteroid administration were screened beyond this period at the discretion of the doctor [1,3]. When a patient developed respiratory symptoms or abdominal symptoms suggestive of CMV disease, bronchoalveolar lavage (BAL) or colonoscopy was performed to determine whether the patient had CMV disease. The patients received preemptive ganciclovir (GCV) at a dose of 5 mg/kg twice