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A Single-Center Experience Comparing Alemtuzumab, Fludarabine, and Melphalan Reduced-Intensity Conditioning with Myeloablative Busulfan, Cyclophosphamide, and Antithymocyte Globulin for Chronic Granulomatous Disease

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A B S T R A C T

Myeloablative conditioning (MAC) regimens are commonly used in transplantation for chronic granulomatous disease (CGD) but are associated with toxicity. Reduced-intensity conditioning (RIC) regimens have lower toxicity but may fail to achieve stable donor chimerism. We report a comparison between 4 patients who received a RIC regimen consisting of alemtuzumab (1 mg/kg), fludarabine (150 mg/m^2), and melphalan (140 mg/m^2) and 14 patients who received a MAC regimen consisting of busulfan (area under the curve, 1800 to 2000 μMol/min twice daily × 4 days), cyclophosphamide (50 mg/kg/day × 4), and antithymocyte globulin (15 mg/kg twice daily on days −2 and −1, then daily on days +1 and +2). Seventy-five percent (n = 3) of RIC patients developed mixed chimerism and needed either withdrawal of immune suppression (n = 1) or additional stem cell products (n = 2) to achieve stable donor chimerism. Ninety-two percent (n = 13) of patients in the MAC group maintained >95% donor chimerism. Complications included acute graft-versus-host disease (MAC 64%, RIC 0%), chronic graft-versus-host disease (MAC 28%, RIC 0%), sinusoidal obstructive syndrome (MAC 7%, RIC 0%), bacteremia (MAC 42%, RIC 0%), fungemia (MAC 14%, RIC 0%), viral disease (MAC 7%, RIC 25%), and death (MAC 21%, RIC 0%). A RIC regimen has lower toxicity but frequently requires interventions to maintain donor chimerism compared with a MAC regimen in CGD.

INTRODUCTION

Chronic granulomatous disease (CGD) is an inherited neutrophil functional defect characterized by recurrent life-threatening infections and autoimmunity [1]. Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative option for CGD in patients with insufficient benefit from supportive care and prophylactic antibiotics [2]. Although myeloablative conditioning (MAC) regimens have been historically used in CGD, reduced-intensity bone marrow transplant conditioning regimens have been increasingly used in patients with significant comorbidities [3-6]. These reduced-intensity conditioning (RIC) regimens aim to reduce transplant-related toxicities and mortality but can be associated with increased risk of developing mixed donor and recipient chimerism or graft loss [3,4,6].

A recent large study in CGD patients (n = 56) of a reduced-toxicity/"submyeloablative" regimen consisting of reduced-dose busulfan, fludarabine, and antithymocyte globulin (ATG) or alemtuzumab was reported to be associated with a 5% incidence of primary or secondary graft failure [7]. Another RIC regimen used for patients with primary immune deficiencies is alemtuzumab, fludarabine, and melphalan. This regimen is nonmyeloablative in many patients and has been used frequently in patients with hemophagocytic lymphohistiocytosis and with various T cell deficiencies, including severe combined immune deficiencies and other combined immune deficiencies [8]. Mixed chimerism is often seen in patients treated with alemtuzumab, fludarabine, and melphalan, with rates ranging from 30% to 70% [8].

In patients with T cell deficiencies or with hemophagocytic lymphohistiocytosis, myeloid chimerism is generally not of great concern, because the aim of the transplant in these patients is usually to replace defects within the lymphocyte compartments. Additionally, in patients with T cell deficiencies there is often a survival advantage for donor-derived T cells that reduce the concern regarding any development of mixed donor and recipient chimerism. Regardless, approximately 5%

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of pediatric and young adult patients who receive alemtuzumab, fludarabine, and melphalan conditioning for treatment of a non-malignant disease have been estimated to ultimately experience graft loss and/or relapse of disease requiring repeat transplantation [8].

In patients with CGD, donor chimerism within the myeloid compartment is the primary concern [1]. Given this, it is important to determine if alemtuzumab, fludarabine, and melphalan RIC HSCT can be used to achieve sustained donor myeloid chimerism in patients with CGD because this regimen would be expected to offer benefit to patients by reducing toxicity and risk of acute graft-versus-host disease (GVHD) compared with traditional MAC. To estimate the success of alemtuzumab, fludarabine, and melphalan RIC HSCT for patients with CGD, we report the outcomes of 4 patients who received alemtuzumab, fludarabine, and melphalan at our center and compare their outcomes with 14 patients who were treated with a myeloablative busulfan, cyclophosphamide, and ATG regimen.

METHODS

The Cincinnati Children's Hospital Medical Center Institutional Review Board granted permission for this retrospective review. Patients with a diagnosis of CGD who received an allogeneic HSCT at Cincinnati Children's Hospital Medical Center between 2006 and 2014 were included. Donors and recipients were HLA matched by high-resolution molecular typing at class I (A, B, C) and class II (HLA DRB1) loci.

MAC regimens were considered the regimen of choice in patients with CGD at our center early on. The combination of busulfan, cyclophosphamide, and ATG was known to achieve successful myeloablation and donor engraftment and was used routinely in patients with CGD across North America and Europe. We therefore used this combination of drugs for our myeloablative approach. Because of limited publications describing RIC regimens and our experience with the successful use of alemtuzumab, fludarabine, and melphalan for primary immune deficiencies, we attempted to offer this reduced-intensity regimen to patients with significant comorbidities and/or to patients in whom there was a higher risk of acute GVHD because of donor mismatch.

Conditioning Regimen Details: RIC

Patients received alemtuzumab at 1 mg/kg s.c. administered in divided doses over 5 days starting on day –14 until day –10. All patients received premedications with methylprednisolone, diphenhydramine, and acetaminophen before alemtuzumab and frequently received a test dose of 3 mg if the initial dose of .2 mg/kg/day exceeded this threshold. Fludarabine was administered at 30 mg/m^2 daily i.v. from day –8 to day –4, and a single dose of melphalan at 140 mg/m^2 was administered i.v. on day –3. GVHD prophylaxis included a combination of either cyclosporine or sirolimus with methylprednisolone at 1 mg/kg/day, with the addition of maraviroc in some patients. Cyclosporine or sirolimus were initiated at day –2 and continued until day +100 post-transplant and tapered off if no signs of acute GVHD were observed. Methylprednisolone was initiated on day 0 and tapered on day +21 if no signs of acute GVHD were observed. Maraviroc was initiated on day –3 and continued until day +30 after stem cell infusion.

Conditioning Regimen Details: MAC

Patients received busulfan every 12 hours p.o. or i.v. on day –10 to day –7 at doses determined by busulfan kinetics with a targeted every 12-hour dosing area under the curve (AUC) of 1800 to 2000 μMol/min. Patients received 50 mg/kg cyclophosphamide i.v. daily between day –5 and day –2. Equine (ATG) was administered at 15 mg/kg i.v. twice daily on days –2 and –1 followed by daily dosing on day +1 and day +2. All patients received premedications with methylprednisolone, diphenhydramine, and acetaminophen before ATG infusions. All patients received seizure prophylaxis during busulfan administration with fosphenytoin. GVHD prophylaxis included cyclosporine and methylprednisolone at 1 to 2 mg/kg/day i.v. with the addition of maraviroc in 1 patient. Cyclosporine was initiated on day –3, whereas methylprednisolone was initiated on day +3 and continued until day +21, after which it was tapered off if no evidence of acute GVHD was observed. Maraviroc was started on day –3 and stopped on day +30. Maraviroc was administered on a single-center, nonrandomized, phase I clinical trial to 1 patient who received a RIC regimen and off-study to 1 patient who received a MAC regimen.

Regimen-Related Toxicity

Charts were reviewed for evidence of engraftment syndrome or sinusoidal obstructive syndrome (SOS) after transplant. Engraftment syndrome was defined by Spitzer criteria [9]. Variables used for definition of SOS included a total bilirubin level > 2 μg/dL, right upper quadrant tenderness, and weight gain > 5% of baseline [10]. Imaging results of ultrasound with Doppler were also reviewed, whenever performed, to aid in diagnosis.

Graft-versus-Host Disease

Charts were reviewed for evidence of acute and chronic GVHD until last follow up. Acute GVHD was graded by the treating physician using the modified Glucksberg criteria [11], whereas chronic GVHD was graded using the 2005 National Institutes of Health consensus criteria [12]. Tissue biopsies and pulmonary imaging, which were obtained as clinically relevant by the treating physician, were reviewed.

Whole Blood Donor Chimerism and Neutrophil Oxidative Burst Monitoring

Whole blood donor chimerism was evaluated by short-tandem repeats or fluorescent in situ hybridization. Neutrophil oxidative burst was assessed by the oxidation of dihydrorhodamine 123 using flow cytometry. Administration of donor lymphocyte infusions (DLIs) or CD34$^+$ selected stem cell infusions was reviewed until last follow-up. No preparative agents were used before CD34$^+$ stem cell infusions or DLIs post-transplant. Immune suppression was withdrawn before CD34$^+$ stem cell infusion and DLI and was not restarted in any patient after the infusion.

Infectious Prophylaxis and Monitoring

All patients received i.v. immunoglobulin and antimicrobial prophylaxis including antiviral, antifungal, and *Pneumocystis jirovecii* prophylaxis as per routine clinical practice. Results of clinical microbiologic testing were reviewed for evidence of infectious complications, including blood, bronchoalveolar lavage, and tissue cultures and PCR when applicable, and the results of serial peripheral blood cytomegalovirus, Epstein-Barr virus, BK virus, and adenovirus PCRs until 1 year after transplant.

RESULTS

Patient Characteristics

Fourteen patients of median age 3.18 years (range, .45 to 19.39) received a MAC regimen for HSCT of CGD. Four patients of median age 14 years (range, 2.65 to 20.17) received a RIC regimen HSCT for CGD. Details of demographics are shown in Table 1. All patients had an abnormal neutrophil oxidative burst test before transplant. Mutations observed included *p91phox* in 75% (n = 3) and *p47phox* in 25% (n = 1) of patients in the RIC group. Mutations included *p91phox* in 36% (n = 5), *p67phox* in 14% (n = 2), *p22phox* 7% (n = 1), and *p47phox* in 7% (n = 1) in the 9 MAC patients in whom data were available.

Comorbidities for all patients are shown in Table 2. The rationale for choosing a RIC regimen included significant comorbidities (n = 2), mismatched unrelated donor transplant and desire to avoid acute GVHD (n = 1), and patient preference along with limited reports in the literature regarding the role of a RIC regimen in CGD (n = 1).

Transplant Characteristics

All RIC patients received an unrelated donor allogeneic HSCT, whereas 78% percent (n = 11) of patients who received a MAC regimen received an unrelated donor transplant (Table 1). GVHD prophylaxis in the MAC group consisted of cyclosporine and methylprednisolone in 93% of patients and cyclosporine, methylprednisolone, and maraviroc in 7% of patients (n = 1); in the RIC group this compared with cyclosporine and methylprednisolone in 50% (n = 2); cyclosporine, methylprednisolone, and maraviroc in 25% (n = 1); and sirolimus and methylprednisolone in 25% (n = 1) of patients. The median total nucleated cell dose × 10^8/kg were comparable between the RIC and MAC groups. The median CD34 × 10^6/kg cell dose was 10.22 (range, 2.2 to 11.7) in the RIC group and 5.7 (range, .48 to 15.7) in the MAC group.