Biol Blood Marrow Transplant 20 (2014) 1722–1728

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcomes of Hematopoietic Cell Transplantation in Adult Patients with Acquired Aplastic Anemia Using Intermediate-Dose Alemtuzumab-Based Conditioning

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Article history:
Received 7 May 2014
Accepted 25 June 2014

Key Words:
Aplastic anemia
Alemtuzumab
Allogeneic transplantation
Graft-versus-host disease
Survival

A B S T R A C T

Graft-versus-host disease (GVHD) has no therapeutic benefit after hematopoietic cell transplantation (HCT) for patients with acquired aplastic anemia (AA), and its prevention is highly desirable. We designed a conditioning regimen using an intermediate dose of alemtuzumab (50 to 60 mg) and describe our institutional experience of 41 patients who underwent HCT for AA. The median age at HCT was 37 years (range, 17 to 59). The conditioning regimen was high-dose cyclophosphamide (n = 9) or fludarabine based (n = 32). Additional GVHD prophylaxis was with cyclosporine. With a median follow-up of 3.6 years, overall survival at 3 years was 85%. Survival in patients <40 years and ≥40 years was 96% and 67%, respectively ($P = .04$). Graft failure occurred in 4 (10%) patients; 2 primary and 2 secondary. The cumulative incidences of acute (grades 1 to 2) and chronic GVHD were 27% and 15%, respectively. No patients developed grade 3 to 4 acute GVHD or severe chronic GVHD. The following viral complications were frequent: cytomegalovirus reactivation (79%), herpes simplex (18%), varicella zoster (25%), and BK virus hemorrhagic cystitis (8%). The majority of patients had no significant long-term health issues. This intermediate-dose alemtuzumab-based conditioning regimen results in excellent survival with a favorable impact on GVHD and long-term health outcomes, but close monitoring for viral complications is important.

INTRODUCTION

The goals of hematopoietic cell transplant (HCT) in acquired aplastic anemia (AA) are sustained hematopoietic recovery, minimal regimen-related toxicities, and minimal graft-versus-host disease (GVHD). The most commonly used conditioning regimen in AA is cyclophosphamide and antithymocyte globulin (ATG) with cyclosporine and methotrexate as GVHD prophylaxis [1]. In addition, total body irradiation is often used for unrelated donor transplantations for patients with AA [2-4]. With these strategies, 30% to 40% of patients with AA develop acute and chronic GVHD, resulting in morbidity, mortality, and poor quality of life [1,3,5-7]. Unlike its effect in hematologic malignancies, GVHD has no therapeutic benefit in patients with AA, and prevention of GVHD is one of the most desirable goals of HCT in AA.

Previous studies reported a favorable effect on acute and chronic GVHD in HCT for AA using in vivo anti-CD52 monoclonal antibodies [8,9]. The main concerns with the use of anti-CD52 antibodies include the risk of graft failure and the increased risk of infectious complications [10-12]. In addition to using different dosing schedules, previous studies used a higher dose of anti-CD52 antibodies (75 to 100 mg) [8,9,13]. There is a suggestion that a lower dose of alemtuzumab may result in a lower risk of infectious complications and faster immune reconstitution [14].

To optimize the use of alemtuzumab in HCT for AA at Princess Margaret Cancer Centre, we designed a conditioning regimen with an intermediate dose of alemtuzumab (50 to 60 mg). We previously published preliminary outcomes of 17 patients treated with alemtuzumab-based GVHD prophylaxis [13,15]. This study reports on outcomes of an additional 24 patients, with updated follow-up on previously reported patients.

METHODS

Patients

A total of 41 consecutive patients who received HCT for AA between January 2005 and August 2013 at the Princess Margaret Cancer Center, Toronto, Canada were included in this study. Data were obtained from a blood and marrow transplantation database, and additional information

Financial disclosure: See Acknowledgments on page 1727.

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1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2014.06.033

was collected from computerized records and patient charts. The University Health Network-Research Ethics Board and Cancer Registry Data Access Committee approved this study.

Eligibility for Transplantation

Patients with severe AA (SAA) <40 years, and having a matched sibling donor (MSD) were offered upfront transplantation. The upper age limit for upfront therapy using MSD transplantation for patients with SAA was increased to 60 years in 2010. Patients with nonsevere AA (NSAA) were offered transplantation after failure of immunosuppressive therapy (IST) using a related or unrelated donor. Patients who only had a mismatched related donor (up to 1 antigen mismatch) or matched unrelated donor were eligible for transplantation if they were refractory to or had relapsed after ATG-containing IST.

Graft Source

Although the preferred source of stem cells was bone marrow (BM), peripheral blood grafts were accepted, based on the donor's choice. Thirty-four (83%) patients received BM grafts and 7 (17%) received peripheral blood grafts.

Conditioning Regimen

Between 2005 and 2009, the institutional standard of care for AA patients <40 years with an MSD was conditioning with high-dose cyclophosphamide (50 mg/kg × 4 days from days −5 to −2) with alemtuzumab 50 mg (10 mg, 20 mg, 20 mg on days −8, −7, and −6 respectively) (n = 9, 23%), and those ≥40 years with an MSD or an MUD regardless of age received fludarabine (30 mg/m^2 × 4 days from days −5 to −2) with low-dose cyclophosphamide (10 mg/kg × 4 days from days −5 to −2) and alemtuzumab 60 mg (30 mg × 2 days on days −7 and −6) (Flu-Cy-Cam) (n = 28, 70%). In 2009, Flu-Cy-Cam became our institutional standard of care for all patients with AA receiving HCT (see Appendix in Supplementary Data for the complete protocol). Busulfan replaced low-dose cyclophosphamide in the Flu-Cy-Cam regimen in 3 patients included in this study. One of these patients had monosomy 7, with BM biopsy findings consistent with AA. The other 2 patients had SAA and symptomatic hemolytic paroxysmal nocturnal hemoglobinuria, and these 2 patients also received 200 cGy total body irradiation as a single fraction.

In the first 10 (25%) patients, alemtuzumab was used as an i.v. infusion; however, in 2006, we changed our institutional practice to subcutaneous (SC) alemtuzumab because of evolving data on its improved side effect profile [16–18] and, therefore, the subsequent 31 (75%) patients received SC alemtuzumab. Premedication for alemtuzumab (30 minutes to 1 hour before) included diphenhydramine 50 mg, acetaminophen 650 mg, and dexamethasone 20 mg orally.

GVHD Prophylaxis

Cyclosporin (CsA) was used for GVHD prophylaxis at a dose of 2.5 mg/kg/day i.v. every 12 hours, starting on day −1, titrated to therapeutic trough levels between 200 and 400 μg/L. When patients were able to tolerate oral medications, the i.v. dose was converted to the oral route. Slow CsA tapering was initiated at 6 months after HCT unless mixed chimerism or ongoing GVHD necessitated continuation of IST. Two patients received tacrolimus (titrated to therapeutic levels of 10 to 20 ug/L) instead of CsA because of a history of gum enlargement with CsA. One patient received mycophenolate mofetil instead of calcineurin inhibitors because of end-stage kidney disease at time of HCT [19].

Definitions

The burden of comorbidities was calculated using the HCT comorbidity index (HCT-CI) [20]. Performance status was assessed using the Karnofsky performance score.

The day of stem cell infusion was defined as day 0. Dates of *neutrophil* and *platelet recovery* were defined as the first of 3 consecutive days of an unsupported absolute neutrophil count ≥.5 × 10^9/L and unsupported platelet count ≥20 × 10^9/L, respectively. *Lymphocyte recovery* was defined as the first of 3 consecutive days of an absolute lymphocyte count of ≥.5 × 10^9/L. Patients were evaluable for engraftment if they survived >21 days after HCT. *Primary graft failure* was defined as the absence of absolute neutrophil count of ≥.5 × 10^9/L on 3 consecutive days after 6 weeks and *secondary graft failure* was defined as recovery followed by recurrent pancytopenia with a hypocellular BM in the absence of severe GVHD. *Time-to-RBC* and *platelet transfusion independence* were defined as the time from the date of HCT to the last date of transfusion for each.

Regimen-related toxicities were evaluated from the start of conditioning therapy until 6 weeks after HCT, defined according to the Bearman's criteria [21].

Patients who survived more than 21 and 100 days were evaluable for the occurrence of acute and chronic GVHD, respectively. Acute and chronic GVHD were graded according to modified Gluckberg's [22] and National Institutes of Health consensus criteria [23], respectively.

Bacterial and viral infections were based on culture and PCR, respectively. Invasive fungal infections were defined as per European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [24].

Supportive Care

All patients received antibacterial, antiviral, and antifungal prophylaxis. Antibacterial prophylaxis with ciprofloxacin 500 mg twice daily orally was given until neutrophil engraftment. Antipneumocystis prophylaxis was initiated at the time of hospital discharge and consisted of oral cotrimoxazole 3 times per week orally or inhaled pentamidine 300 mg monthly (if allergic or intolerant to cotrimoxazole) and continued to 1 year after HCT or longer, if the patient was still on IST. Anti–herpes simplex virus (HSV) prophylaxis with acyclovir 400 mg once daily orally was given for 3 months. All patients received antifungal prophylaxis with itraconazole suspension (200 mg orally twice daily for 3 months) until January 2009, after which there was a change in our institutional practice to i.v. micafungin during the hospital stay and a switch on discharge to oral posaconazole suspension 200 mg 3 times a day for 3 months. Routine surveillance of cytomegalovirus (CMV) viremia was performed on a weekly basis for the first 100 days and subsequently on clinic visits up to 1 year or according to clinical need. This was done using pp65 antigenemia until 2011 and, thereafter, this was performed using PCR. Ganciclovir was used as preemptive treatment in patients testing positive for CMV viremia. Pulmonary function tests (PFTs) were routinely performed at baseline, 4 and 12 months after HCT, and annually thereafter. Hormone profiles including sex hormones, prolactin, and thyroid function tests were also done annually.

Chimerism and Disease Monitoring

Chimerism studies were performed on whole blood by short tandem repeat (STR)-PCR analysis. Testing was carried out at 30, 60, and 120 days after HCT routinely, and according to clinical need thereafter. Donor cells ≥90% were considered as predominantly donor chimerism (PDC) and <90% as mixed chimerism (MC). *Declining donor chimerism* was defined as a ≥10% decrease in donor chimerism on 2 consecutive measurements. In cases of MC, an increase in the intensity of IST was attempted.

Statistical Methods

Categorical variables were summarized with counts and percentages and continuous variables with medians and ranges or standard deviations, as appropriate. Time-to-reach hematologic endpoints were calculated using primary engraftment failure and death as competing endpoints. The incidence of infection was calculated using the cumulative incidence method with death and second HCT as a competing end point. The probability of overall survival (OS) was calculated with the Kaplan-Meier method. Univariate analysis was performed on OS using binary clinical factors with Kaplan-Meier curves and log-rank tests. Because of the small number of events, a multivariate analysis was not performed. All analysis was performed using R Version 3.0.1 (R Development Core Team).

RESULTS

Baseline patient-, disease-, and transplantation-related characteristics are summarized in Table 1. The median age at HCT was 37 years (range, 17 to 59). The majority of patients had SAA: 12 (29%) very severe AA, 19 (46%) SAA, and 10 (24%) NSAA. Patients with NSAA had failed IST and were transfusion dependent. Donors were HLA MSD in 29 (70%) and MUD in 12 (30%). Median follow-up of survivors was 3.6 years (range, .13 to 7.9).

Side Effects of i.v. and SC Alemtuzumab

Side effects of i.v. alemtuzumab (n = 10) were infusion-related rigors/chills (n = 6, 60%), fever (n = 4, 40%), generalized skin rash (n = 3, 30%), chest tightness (n = 1, 10%), and hypotension (n = 1, 10%). With SC alemtuzumab (n = 31), side effects were self-limiting erythema at injection site (n = 26, 84%), generalized skin rash (n = 3, 10%), and fever (n = 2, 6%). None of the patients discontinued alemtuzumab because of side effects.

Regimen-related Toxicities

The majority of patients tolerated the conditioning well. None of the patients had grade 3 toxicities. Bearman grade 1