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Long-Term Outcomes of Alemtuzumab-Based Reduced-Intensity Conditioned Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome and Acute Myelogenous Leukemia Secondary to Myelodysplastic Syndrome

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) with reduced-intensity conditioning (RIC) offers a potential cure for patients with myelodysplastic syndrome (MDS) who are ineligible for standard-intensity regimens. Previously published data from our institution suggest excellent outcomes at 1 yr using a uniform fludarabine, busulfan, and alemtuzumab-based regimen. Here we report long-term follow-up of 192 patients with MDS and acute myelogenous leukemia (AML) secondary to MDS (MDS-AML) transplanted with this protocol, using sibling (n = 45) or matched unrelated (n = 147) donors. The median age of the cohort was 57 yr (range, 21 to 72 yr), and median follow-up was 4.5 yr (range, 0.1 to 10.6 yr). The 5-yr overall survival (OS), event-free survival, and nonrelapse mortality were 44%, 33%, and 26% respectively. The incidence of de novo chronic graft-versus-host disease (GVHD) was low at 19%, illustrating the efficacy of alemtuzumab for GVHD prophylaxis. Conversely, the 5-yr relapse rate was 51%. For younger patients (age <50 yr), the 5-yr OS and relapse rates were 58% and 39%, respectively. On multivariate analysis, advanced age predicted significantly worse outcomes, with patients age >60 yr having a 5-yr OS of 15% and relapse rate of 66%. Patients receiving preemptive donor lymphocyte infusions had an impressive 5-yr OS of 67%, suggesting that this protocol may lend itself to the incorporation of immunotherapeutic strategies. Overall, these data demonstrate good 5-yr OS for patients with MDS and MDS-AML undergoing alemtuzumab-based RIC-HSCT. The low rate of chronic GVHD is encouraging, and comparative studies with other RIC protocols are warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) secondary to MDS (MDS-AML). The development of reduced-intensity conditioning (RIC) regimens has extended this treatment modality to older patients and those with comorbidities. Post-transplantation survival estimates range from 20% to 60%, with variation related to MDS subtype, disease risk, cytogenetics, and conditioning intensity [1-4]. Despite major advances in supportive care and decreases in nonrelapse mortality (NRM), relapse and graft-versus-host disease (GVHD) remain major limitations to the long-term success of this procedure. High rates of chronic GVHD (cGVHD), on the order of 40% to 52%, have been reported [5,6], a problem compounded by the need for continuing immunosuppression and complications related to prolonged corticosteroid administration.

Even though the first report of HSCT for MDS was published many years ago, data on long-term outcomes of RIC-HSCT for MDS remain limited. Registry studies contain heterogeneous populations and varied conditioning protocols. The use of T cell depletion (TCD) as part of the RIC protocol has the potential to decrease rates of GVHD, thus further improving NRM and quality of life. Concerns associated with this approach include a decreased graft-versus-leukemia effect, particularly with RIC protocols [6], and increased rates of infection, particularly of viral infections, such as cytomegalovirus (CMV). Pharmacologic TCD is generally achieved with either antithymocyte globulin or alemtuzumab, a monoclonal antibody directed against CD52. Early data from our institution demonstrate excellent outcomes at 1 yr with fludarabine and busulfan combined with alemtuzumab (FBC) in sibling and unrelated donor allografts [7]. Here we present the largest single-institution analysis to date of long-term outcomes of 192 patients who underwent RIC-HSCT for MDS or MDS-AML using a uniform alemtuzumab-based RIC protocol.

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MATERIALS AND METHODS

Medical records of all patients with MDS or MDS-AML receiving an FBC-based protocol between 1999 and 2009 were identified. MDS-AML was diagnosed based on the presence of previous MDS or morphological

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dysplasia at the time of AML diagnosis. All diagnostic specimens were reviewed by specialist hematopathologists. Cytogenetic categories were allocated according to the International Prognostic Scoring System (IPSS) for MDS and European Leukaemia Net recommendations for patients with MDS-AML. In view of the recent publication of a revised cytogenetic classification system for MDS [8], patients were also categorized according to this system to evaluate their potential for additional stratification in the setting of RIC-HSCT.

The FBC RIC protocol includes 30 mg/m^2 fludarabine i.v. (on days −9 to −5); 4 mg/kg busulfan orally or 3.2 mg/kg i.v. (on days −3 to −2), and 20 mg alemtuzumab i.v. (on days −8 to −4). All patients with an excess of blasts were treated with the aim of achieving <5% blasts before HSCT. Donors were fully HLA-matched siblings, matched unrelated donors (MUDs), or 1-antigen-mismatched unrelated donors. Hematopoietic stem cells from either peripheral blood stem cells (PBSCs) or bone marrow (BM) were infused on day 0. Immunosuppression was achieved with 1.5 mg/kg cyclosporin i.v. twice daily starting on day −1, with the dose titrated to maintain a plasma trough level of 150 to 200 ng/L. The i.v. cyclosporin was changed to the oral form when clinically appropriate and tapered from day +56 in the absence of GVHD, with the aim of stopping cyclosporin by day +100.

All patients received standard anti-infective prophylaxis in accordance with institutional guidelines. Recipients were screened weekly for CMV reactivation as described previously [7] for the first 6 mo, then every 2 weeks until immunosuppression was completely withdrawn and no GVHD was present.

Chimerism was assessed by XY fluorescence in situ hybridization when a donor–recipient sex mismatch existed and/or by PCR and fluorescent analysis of short tandem repeat sequences on BM, whole blood, and peripheral blood CD3 and CD15 cell fractions. Chimerism assessment was scheduled for days +28, +56, +100, and +180 and then every 6 months thereafter. Preemptive donor lymphocyte infusion (pDLI) was administered in the presence of evidence of recipient chimerism (donor CD3 <95%) despite withdrawal of immunosuppression or decreasing donor CD3 by >20% over 1 mo. DLI was also administered therapeutically (tDLI) as part of treatment for relapsed disease.

Response was assessed morphologically and, when a previous karyotypic abnormality was present, by conventional cytogenetics. Diagnosis of relapse in patients with a primary diagnosis of refractory anemia (RA) or refractory cytopenia with multilineage dysplasia (RCMD) required evidence of dysplasia by BM morphology in combination with cytopenias or reemergence of a previous cytogenetic abnormality. Increasing recipient chimerism provided supportive evidence of relapse in this context.

GVHD was assessed based on guidelines of the Consensus Conference on GVHD Grading and confirmed histologically when possible. CGVHD was classified according to consensus criteria [9]. De novo GVHD was defined as onset of GVHD before DLI administration. Graft failure was defined as a neutrophil count $<0.5 \times 10^9$/L beyond day +28 and/or evidence of loss of donor cells on the basis of cytogenetics or chimerism studies in the absence of relapse. Overall survival (OS) was measured from day 0 to death from any cause; event-free survival (EFS), from day 0 to the first indicator of relapse, graft failure, or death; and nonrelapse mortality (NRM), from day 0 to death without evidence of relapse.

Statistical analyses were performed using SPSS version 20 (IBM, Armonk, NY). Survival curves for the entire cohort were generated by the Kaplan-Meier method. The log-rank test was used to assess the effect of variables including age, sex, disease group (World Health Organization category), IPSS, Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) (0 versus 1 versus ≥2), cytogenetic risk, disease status at time of transplantation (complete remission versus >5% blasts), donor type (sibling versus MUD), HLA disparity, and source of stem cells (PBSCs versus BM) on OS, EFS, relapse, and NRM. Variables included in multivariate analysis were those displaying significant association with a transplantation outcome in univariate analysis. The Cox proportional hazards model was used for multivariate analysis; independent variables with $P = .10$ were sequentially excluded from the model. The P value was set at .05 for statistical significance. A competing-risk analysis was performed to assess the effect of cGVHD on relapse.

RESULTS

A total of 192 consecutive patients (86 females, 106 males) with MDS and MDS-AML receiving FBC RIC-HSCT were identified. Patient characteristics are detailed in Table 1. Median follow-up was 4.5 yr (range, 0.1 to 10.6 yr), and median age of the cohort was 57 yr (range, 21 to 72 yr). Diagnoses included RA, RCMD, refractory anemia with excess of blasts (RAEB), chronic myelomonocytic leukemia (CMML), and MDS-AML. All 86 patients with MDS-AML received high-dose combination chemotherapy before transplantation. Of 46 patients with RAEB, 40 patients received combination chemotherapy, 4 received 5-azacitidine and 2 received no treatment. Of 12 patients with CMML, 11 received combination chemotherapy and 1 received no treatment. Nine of the 48 patients with RCMD received a single course of combination chemotherapy, 11 patients had received previous immunosuppressive therapy, 9 patients had failed erythropoietin. and 19 patients received no treatment.

Table 1
Patient Demographic Data

Characteristic	Value
No. of patients	192
Age, yr, median (range)	57 (21-72)
Age group, n (%)	
<50 yr	55 (29)
50-60 yr	72 (37)
>60 yr	65 (34)
Diagnosis, n (%)	
RCMD/RARS	48 (25)
RAEB	46 (24)
MDS-AML	86 (45)
CMML	12 (6)
IPSS category, n (%)	
Low	8 (4)
Int-1	42 (22)
Int-2	35 (18)
High	9 (5)
AML	86 (45)
Cytogenetics, n (%)	
Good	63 (33)
Intermediate	92 (48)
Poor	32 (17)
Donor type, n (%)	
Sibling	44 (23)
MUD	148 (77)
HLA match, n (%)	
Matched	151 (79)
1 antigen mismatched	41 (21)
Stem cell source, n (%)	
BM	51 (26)
PBSCs	141 (74)
HCT-CI, n (%)	
0	48 (25)
1	40 (21)
≥2	100 (52)
Status at transplantation, n (%)	
No chemotherapy	37 (19)
CR1	122 (64)
≥CR2	24 (13)
>5% blasts	9 (5)

OS and EFS

Data for 1- and 5-yr OS, EFS, and relapse are summarized in Tables 2 and 3. For the entire cohort, 5-yr OS was 44% and 5-yr EFS was 33% (Figure 1A and B). Univariate analysis identified no significant difference for OS or EFS for donor type (sibling versus MUD), HLA match (10/10 versus 9/10), and cytogenetic category (good versus intermediate versus poor). Patients with an HCT-CI of 0 had better OS and EFS than patients with an HCT-CI of ≥2 (OS, 59% versus 33% versus 40%; $P = .06$; EFS, 48% versus 31% versus 24%; $P = .008$). Greater than 5% blasts at time of transplantation was significantly associated with poorer OS and EFS ($P < .001$). There was a trend toward poorer OS for patients with higher IPSS scores and significantly worse 5-yr OS and EFS for patients with RAEB (OS, 24%, $P = .008$; EFS, 9%, $P = .001$) and CMML (OS, 25%, $P = .006$; EFS, 25%, $P = .08$) versus RA/RCMD (OS, 57%; EFS, 48%). For EFS, patients