INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (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 [3,4] 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.

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...
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 [9], 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/m² fludarabine i.v. (on days 9 to 15); 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. pDLI 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 x 10⁹/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), HLA match, and cytogenetic category (good versus intermediate versus poor). 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% [Figure 1A and B]. Univariate analysis identified no significant difference for OS or EFS for 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. 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.

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
categorized as IPSS int-2 and high risk had significantly worse outcomes compared with those classified as low risk (P = .01). With regard to OS and EFS, younger patients had improved outcomes compared with patients age > 60 yr; (Figure 2) 5-yr OS was 56% for patients age 50 to 60 yr, 58% for those age 50-60, and 55% for patients age >60 yr, respectively. When this group was analyzed separately, age was the sole factor retaining significance for both OS and EFS (for OS: relative risk [RR], 2.5; 95% confidence interval [CI], 1.8 to 3.8; for age >60 yr: RR, 2.9; 95% CI, 1.2 to 7.3 for blasts >5%; for EFS: RR, 1.9; 95% CI, 1.3 to 2.8 for age >60 yr and RR, 3.5; 95% CI, 1.5 to 8.2 for >5% blasts).

A landmark analysis performed on patients alive at 1 yr (n = 108) demonstrated 5-yr OS and EFS of 72% and 54%, respectively. When this group was analyzed separately, age was the sole factor retaining significance for OS with 5-yr OS of 36% for patients age >60 yr compared with 80% for patients age <60 yr at the time of transplantation: RR, 4.0 (95% CI, 1.8 to 9.1) for age >60 yr. For EFS, both age and HCT-CI were significant on multivariate analysis: RR, 2.5 (95% CI, 1.3 to 5.0) for age >60 yr and RR, 1.3 (95% CI, 1.0 to 1.7) for HCT-CI >0.

**Table 2**

<table>
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<tr>
<th>Age, yr</th>
<th>OS, % (95% CI) P Value</th>
<th>EFS, % (95% CI) P Value</th>
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<td>70 NS 56 NS 38 NS</td>
<td>.90 .01</td>
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<td>&gt;60</td>
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**Diagnosis**

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<td>75 75</td>
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<tr>
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<td>Int-1</td>
<td>66 52</td>
<td>NS 50</td>
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<td></td>
<td>Int-2</td>
<td>65 38</td>
<td>NS 40</td>
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<tr>
<td></td>
<td>High</td>
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<tr>
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<td>NS 55</td>
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**Cytogenetics**

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**Stem cell source**

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</tr>
<tr>
<td>BM</td>
<td>59 48</td>
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**HCT-CI**

|        | 73 59  |
|--------| 63 48  |
| <2     | 55 33  |
| >2     | 56 40  |

**Status at transplantation**

| No chemotherapy | 80 70  |
| CR1          | 58 40  |
| >CR2        | 62 42  |

**Remission status**

|        | <.001 11 0 <.001 |
| <5% blasts | 63 46 51 33  |
| >5% blasts  | 30 0   |

NS indicates not significant.

- Patients who received no chemotherapy had low-risk MDS (RCMD/RA) and <5% blasts.
- For CR1 versus >CR2.

**Relapse**

The 5-yr relapse rate for the entire cohort was 51% (Figure 1C). No significant effect was found for donor type, stem cell source, degree of HLA match, or cytogenetics, whereas in patients with high IPSS score, diagnosis of RAEB or CMML versus RA/RAMD, age >60 yr, HCT-CI >2, and >5% blasts at the time of transplantation had worse outcomes in terms of relapse (Table 3). On multivariate analysis, age, >5% blasts and HCT-CI retained significance (RR, 1.9 [95% CI, 1.2 to 3.2] for age >60 yr; RR, 6.4 [95% CI, 2.7 to 15.0] for >5% blasts at time of transplantation; and RR, 1.3 [95% CI, 1.0 to 1.6] for HCT-CI >0).

Patients who relapsed before 100 d, before 365 d, and after 1 yr were analyzed in an attempt to identify predictors of early relapse. Of 19 patients who relapsed before day 100, 12 (63.2%) were age >60 yr, compared with 6 patients (31.6%) age 50 to 60 yr and only 1 patient (5.3%) age <50 yr (P = .01). No difference was found for diagnosis (RA/RAMD versus RAEB versus AML versus CMML), cytogenetics, IPSS, remission status (compete remission [CR] 1 versus CR2), or >5% blasts pretransplantation. Although these values were not statistically significant, likely owing to small numbers on stratification, of note, 5 of 9 patients with >5% blasts at the time of transplantation (56%) had relapsed before day 100 and 8 (89%) had relapsed before 1 yr.
Effect of Revised Cytogenetic Criteria

An additional analysis performed to evaluate the effect of the revised cytogenetic criteria in patients undergoing HSCT with a diagnosis of MDS (n = 94) revealed significantly worse outcomes (P < .001) in terms of both OS and EFS in patients with very-poor-risk cytogenetics (n = 6) compared with those in all other categories. No patients in this cohort were classified in the very-good-risk cytogenetic group. Median OS and EFS post-HSCT for the very-poor-risk group was low, 155 d (range, 50 to 363 d) and 83 d (range, 50 to 242 d), respectively.

Relapse rates were significantly worse for the patients with very-poor-risk cytogenetics compared with those with good-risk (n = 55) and intermediate-risk (n = 23) patients, but not compared with poor-risk patients (n = 10). All very-poor-risk patients had relapsed within 8 mo (the earliest at day +83), and 78% of poor-risk patients had relapsed by 25 mo (earliest at day +63 d). Patients with very-poor-risk cytogenetics also had worse NRM, with a day +100 NRM of 34%, compared with 10% for poor-risk (P = .06), 0% for intermediate-risk (P = .01), and 2% for good-risk (P = .008) patients.

Engraftment and Chimerism

The majority of patients (n = 141) received PBSCs at median dose of $6.40 \times 10^8$/kg (range, 1.09 to $17.5 \times 10^8$/kg). Fifty-one patients received BM at a median dose of $2.59 \times 10^8$/kg (range, 0.44 to $13.7 \times 10^8$/kg). Neutrophil and platelet engraftment occurred at a median of 13 d and 15 d, respectively. Graft failure occurred in only 14 patients (7% primary in 7 and secondary in 7). Eight of those 14 patients underwent a second transplantation, 3 of whom were alive at the time of this report. Five patients died of complications secondary to graft failure, and 1 patient was alive with autologous reconstitution.

Data on CD3 chimerism were available for 103 patients at day +28, 117 patients at day +100, 90 patients at day +180, and 82 patients at 1 yr. Rates of mixed T cell chimerism were at 63.1% at day +28, 62.2% at day +56, 57.3% at day +100, 52.2% at day +180, and 47.6% at 1 yr.

NRM and Causes of Death

Data for NRM are summarized in Table 3. NRM was 5% at 100 d and 20% at 1 yr. Overall NRM at 5 yr remained low at 26% (Figure 1D). Donor type, degree of HLA matching, HCT-CI, IPSS, cytogenetics, and World Health Organization category had no significant association with NRM. Advanced age was associated with higher rates of NRM, with a 1-yr NRM of 33% and a 5-yr NRM of 48% in patients age >60 yr, compared with 14% and 20% in patients age 50 to 60 yr and 15% and 18% in patients age <50 yr (P = .01).

At the time of censoring, 101 patients had died. Cause of death included relapse in 52, GVHD in 10, sepsis in 9, multiorgan failure in 5, fungal infection in 2, graft failure in 6, cerebral hemorrhage in 2, veno-occlusive disease in 2, post-transplantation lymphoproliferative disorder (PTLD) in 2, CMV pneumonitis in 1, disseminated adenovirus and CMV hepatitis in 1, pulmonary embolism in 1, and definitive cause unidentifiable in 8.

Acute and Chronic GVHD

Acute GVHD (aGVHD) was diagnosed in 66 patients (34%), 39 with grade III-IV aGVHD (20%). De novo cGVHD occurred in only 37 patients (19%). According to National Institutes of Health criteria, the global grade of cGVHD was moderate in 13 patients (6.5%) and severe in 7 (3.5%). Five patients (2.5%)
were classified as having overlap syndrome of GVHD. Death was attributed to GVHD in only 2 of the 13 patients with moderate GVHD, compared with 2 of the 7 patients with severe cGVHD. All patients with overlap syndrome subsequently died, 2 from relapse, 1 from sepsis, 1 with multiple cerebral lesions (definitive cause not identified), and 1 from GVHD (skin/gut). A competing-risk analysis performed to assess the effect of de novo cGVHD on relapse (with death as competing risk) demonstrated no association of cGVHD with decreased relapse.

**DLI**

DLI was administered to 73 patients (38%). The majority of these patients (n = 44; 60%) received pDLI for falling or inadequate CD3 chimerism, whereas the remainder (n = 29; 40%) received tDLI as treatment for relapsed disease. In the patients who received pDLI, the median CD3 before DLI was 20% (range, 0 to 59%), and the median time to DLI was 169 d (range, 87 to 1297 d). Patients received a median of 2 courses (range, 1 to 5), with a median dose of 5.5 x 10^6 CD3 cells/kg (range, 5 x 10^5 to 1.66 x 10^8 CD3 cells/kg). In the patients who received tDLI, the median CD3 before DLI was 87% (range, 7% to 100%), and the median time to DLI was 256 d (range, 74 to 1304 d). Patients received a median of 2 courses (range 1 to 8) with a median dose of 6.5 x 10^6 CD3 cells/kg (range, 5 x 10^5 to 1.43 x 10^8 CD3 cells/kg). Of the patients receiving pDLI, 30 (68%) attained full donor chimerism (FDC), 4 (8%) attained stable mixed chimerism, and 10 (23%) had no response. Of the patients who received tDLI, 6 (21%) achieved long-term remission, 4 (14%) attained CR and then subsequently relapsed, and 19 (65%) did not respond. Thirty-three patients (46%) developed GVHD post-DLI. The patients who received pDLI had a 5-yr OS of 67%, compared with 37% in those receiving tDLI. Ten patients age >60 yr received pDLI; these patients had a 5-yr OS of 67%, similar to that in patients age <60 yr.

**CMV and PTLD**

A total of 119 patients were considered at risk for CMV reactivation on the basis of donor or recipient serology. Of these, 75 patients (63%) developed CMV reactivation. Only 8 patients (4%) had CMV disease (2 with hepatitis, 4 with pneumonitis, and 2 with colitis). Overall, there were 3 documented cases of biopsy-proven PTLD, of whom 2 died and 1 was successfully treated with rituximab.

**DISCUSSION**

To our knowledge, this study comprises the largest cohort of patients with MDS and MDS-AML treated with uniform alemtuzumab-based RIC-HSCT reported to date. We found favorable long-term outcomes with high OS and, importantly, low NRM and rate of GVHD in patients age <60 yr. In other alemtuzumab-based protocols, long-term survival estimates have ranged from 31% at 3 yr to 45% at 4 yr [10-12]. A recent large Center for International Blood and Marrow Transplant Research (CIBMTR) analysis reported 5-yr OS of 33% for RIC protocols (mainly T cell replete) and a European Group for Blood and Marrow Transplantation analysis reported a 4-yr OS of 31% in patients age >50 yr [13]. Our reported 5-yr OS of 44% for our entire cohort compares favorably with the results of those studies. In addition, our landmark analysis of patients alive at 1 yr, indicating excellent long-term survival, suggests low rates of later complications with this protocol.

Of note, high rates of OS and EFS (46% and 39%, respectively) were observed for our patients with MDS-AML (Figure 3), a group traditionally associated with poorer prognoses. Young patients with MDS-AML had a 5-yr OS of 65% and 5-yr EFS of 55%. Younger patients and those with low-risk disease did particularly well on this protocol, with a 5-yr OS of 74% and 5-yr EFS of 55% in patients age <50 yr and those with RCMD/RA. This finding compares well with the OS reported in other low-risk cohorts [14] and suggests that
transplantation for lower-risk disease is a viable option, resulting in sustained long-term remissions.

Of particular significance in this study are the low rates of aGVHD and cGVHD, indicating that long-term survival is achievable without the potentially debilitating effects of cGVHD. Only 20 patients (10%) had moderate or severe de novo cGVHD, and only 10 patients (9.9%) had death attributable to any form of GVHD (acute, chronic, or post-DLI), despite the fact that the majority of patients (77%) received stem cells from an unrelated donor. This protocol is also associated with a low NRM of only 5% at 100 d and 20% at 1 yr. Of note, NRM did not continue to increase significantly in the subsequent years, with a 5-yr NRM of 26% for the entire cohort. This finding likely reflects the low rate of cGVHD, and suggests that TCD does not lead to longer-term infection-related mortality. This suggestion is supported by the low number of patients with death attributed to infection, 12% (<1%) at the time of censoring.

A major concern with the use of TCD is an increased rate of viral infection, particularly CMV [15]. In our analysis, although 63% of the patients at risk developed CMV reactivation, the rate of clinically important CMV disease was extremely low, occurring in only 4% and contributing to death in only 2 patients (<1%). Furthermore, PTLD was diagnosed in only 3 patients.

Although the rates of GVHD are low in the FBC protocol, the relapse rates are of concern. The majority of relapses occurred in the first year post-transplantation, particularly in patients with high-risk disease features, such as high IPSS score, RAEB versus RCMD, older age, and poor-risk cytogenetics (Table 3). Despite the observed 5-yr relapse rate of 51%, OS remained good for this cohort, suggesting that although relapse occurs, a number of patients can be salvaged. This is illustrated by the 5-yr OS of 37% in patients receiving DLI for relapse, a figure considerably better than reported for most patients who relapse post-transplantation [16]. Indeed, patients who received pDLI to revert low or falling donor chimerism demonstrated a very good 5-yr OS of 67%, suggesting that this protocol may lend itself to the incorporation of immune therapies, such as DLI, that can promote long-term OS post-transplantation. A more detailed analysis of the use of DLI in the TCD setting by our group supports this theory [17], demonstrating excellent long-term outcomes in patients with MDS or AML after pDLI. In view of these findings, current recommendations in our institution are to administer pDLI as the standard of care for patients with low or falling chimerism, with a prospective clinical trial planned to further substantiate these findings.

Our results confirm those from previous studies [18,19], indicating that remission status at the time of transplantation is important for OS and EFS. Although only 9 of our patients had >5% blasts at the time of transplantation, none of these patients was alive and free of disease at 5 yr, and all but 1 had relapsed within 1 yr. For these patients, whether results may be improved by increasing the busulfan component of this protocol or by altering TCD is unclear.

Although we failed to demonstrate a significant impact of IPSS cytogenetics on outcomes, reclassification of the group according to revised cytogenetic criteria demonstrated poorer outcomes and short median survival for those with very-poor-risk cytogenetics. Although this group of patients was small, this finding emphasizes the importance of applying refinements in disease stratification to patient selection for transplantation, allowing more accurate prediction of post-transplantation outcomes. Future studies incorporating this knowledge will be important with respect to developing novel therapies or intensifying post-transplantation strategies aimed at relapse prevention.

Outcomes in patients age >60 yr were inferior, with higher rates of relapse and NRM contributing to lower OS and EFS. Reasons for this were not definitively identifiable; these patients did not have significant differences in terms of adverse prognostic factors, such as poor-risk cytogenetics or greater proportion of higher HCT-CI scores, compared with the remainder of the group. Advanced age retained the greatest significance on multivariate analysis for both OS and EFS; thus, it is possible that unmeasured factors relating to disease biology or immune reconstitution are important in the elderly. Of note, the majority of the 19 patients who relapsed before 100 d post-HSCT were age >60 yr.

Poorer outcomes in patients age >60 yr receiving alemtuzumab in combination with melphalan have been reported previously [20]; however, our data relating to age conflict with findings from a recent large CIBMTR analysis of non-myeloablative and RIC HSCT [21]. Most patients in the CIBMTR analysis did not receive TCD, possibly contributing to the different outcomes. It is conceivable that the effect of TCD might be more pronounced in the elderly population, in whom immune reconstitution is already compromised [22-24]. Strategies to address this effect include decreasing the alemtuzumab dose, an approach shown to be feasible in other studies [25,26], or using pDLI, which we found to result in sustained remissions as outlined above. Interestingly, in the data presented herein, although the number of patients age >60 yr who received pDLI was small, the 5-yr OS was high at 67%.

In summary, this analysis demonstrates very good long-term outcomes for patients age <60 yr receiving FBC RIC-HSCT, with low rates of NRM and GVHD despite the predominantly unrelated donor setting. Although relapse is an issue, this protocol provides an ideal basis for RIC-HSCT, and can act as a platform for subsequent immune therapies such as DLI, resulting in sustained remissions. Future directions could involve prospective trials assessing the value of busulfan dose intensification, early pDLI, or use of adjunctive post-transplantation pharmacotherapeutic strategies to minimize relapse.

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REFERENCES


