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Haploidentical

Fludarabine and Total-Body Irradiation Conditioning before Ablative Haploidentical Transplantation: Long-Term Safety and Efficacy

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Although myeloablative conditioning (MAC) before haploidentical donor transplant (HIDT) with post-transplant cyclophosphamide is being increasingly used, the optimal preparative regimen remains unclear. In our initial trial, the feasibility of HIDT following a MAC preparative regimen using fludarabine and 12 Gy of total-body irradiation was demonstrated in 30 patients. We now present long-term outcome results, including an additional 52 patients, now with 47 months (16 to 96) median follow-up. Median patient age was 42 (19 to 61) years. The most common diagnoses were acute myelogenous leukemia (51%) and acute lymphoblastic leukemia (33%), and 39% had a high/very high disease risk index (DRI). Engraftment was universal with no cases of primary or secondary graft failure. Grade 3 to 4 acute graft-versus-host disease (GVHD) and moderate to severe chronic GVHD occurred in 17% and 23%, respectively. Nonrelapse mortality (NRM) was 7% at 1 year and 13% at 4 years. Estimated 4-year overall survival (OS), disease-free survival, and cumulative incidence of relapse (CIR) were 67%, 60%, and 27%, respectively. CIR was significantly higher in patients with high/very high- versus low/intermediate-risk DRI (38% versus 20%, $P = .032$), which led to inferior 4-year OS (50% versus 77%, $P = .001$). Median time to systemic immunosuppressive therapy (IST) discontinuation was 7.8 months, with 84% of patients off IST at 2 years post-transplant. Current GHVD-free, relapse-free survival (CGRFS) at 2, 3, and 4 years was 60%, 57%, and 60%, respectively. This approach to MAC HIDT results in universal engraftment; low rates of NRM, infection, and clinically significant GVHD; and relatively rapid IST discontinuation, resulting in high rates of CGRFS and survival.

INTRODUCTION

T cell replete haploidentical donor transplantation (HIDT) using post-transplant cyclophosphamide (PTCy) has emerged as a safe and effective alternative for patients without an available HLA-matched related or unrelated donor [1-4]. As a result, the number of HIDTs performed in the United States and Europe has increased rapidly in recent years [5,6]. The original experience of HIDT-PTCy used a reduced-intensity conditioning (RIC) regimen consisting of fludarabine, cyclophosphamide, and low-dose total- body irradiation (TBI; 200 cGy) with bone marrow used exclusively as the graft source. In this setting, graft-versus-host disease (GVHD) and nonrelapse mortality (NRM) rates were low [3,4], but relapse remained a significant problem and the predominant cause of treatment failure [3,7]. In addition, the incidence of primary or secondary graft failure was approximately 8%, with the majority of patients achieving autologous recovery [8].

In more recent years, myeloablative conditioning (MAC) regimens have been used for HIDT-PTCy in an effort to decrease relapse rates and improve engraftment, and multiple reports have demonstrated the feasibility of this approach [9-13]. We previously developed an approach to MAC HIDT-PTCy using fludarabine and TBI 12 Gy pretransplant, a T cell replete peripheral blood stem cell (PBSC) graft, and PTCy, tacrolimus, and mycophenolate mofetil and reported the results of a 30-patient feasibility study [13]. The current analysis includes an additional 52 patients treated in an identical manner, outside of a clinical trial, with 4 years of median follow-up. Our objective in this report was to assess the long-term safety and efficacy of this approach, supplemented with several new analyses, including time to systemic immunosuppressive therapy (IST) discontinuation; GVHD-free, relapse-free survival (GRFS); current GRFS (CGRFS); and disease-specific survival outcomes.

PATIENTS AND METHODS

Patient Characteristics

Institutional review board approval was granted for this retrospective review of 82 consecutive patients who received MAC HIDT-PTCy between May 2011 and December 2017. The cohort included the 30 patients treated in our previously published phase 2 study [13]. Following the completion of

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this study, this fludarabine/TBI regimen became our institutional standard-of-care conditioning for patients ≤60 years of age with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), or other poor-risk hematologic malignancy deemed to be at high risk for post-transplant relapse. Median follow-up for surviving patients was 47 months (range, 16 to 95 months) at the time of analysis. Baseline characteristics were prospectively recorded in our institutional database, and events (graft failure, relapse, death, cause of death, acute and chronic GVHD) were entered into the database prospectively. These data were retrospectively extracted from the database at the time of analysis.

Treatment Plan

Transplant conditioning for all patients consisted of fludarabine 30 mg/m^2/d on days −7 to −5 and TBI 150 cGy bid on days −4 to −1 (total dose 1200 cGy). On day 0, patients received an unmanipulated PBSC allograft with a CD34 dose capped at 5×10^6/kg recipient weight. On day +3 and +4, patients received 2 doses of cyclophosphamide (Cy) 50 mg/kg/d with Mesna. Post-transplant immunosuppression was initiated on day +5 with intravenous tacrolimus (target level 5 to 15 ng/mL) and oral mycophenolate mofetil (MMF) (15 mg/kg 3 times daily with a maximum daily dose of 3 g). No immunosuppressive agents were administered until 24 hours following the last dose of post-transplant Cy, including corticosteroids. MMF and tacrolimus were planned to discontinue without taper at days +35 and +180, respectively, in the absence of GVHD, although early discontinuation was permitted by physician discretion in patients with a perceived high risk of post-transplant disease recurrence or in those experiencing early post-transplant relapse of disease.

Antimicrobial prophylaxis was administered according to institutional practice guidelines. Standard prophylaxis was started on day 0, including a quinolone antibiotic and acyclovir. Antifungal prophylaxis consisted of an echinocandin (eg, micafungin) until day +5, when the patient was started on oral therapy with voriconazole, posaconazole, or isavuconazole. Filgrastim 5 μg/kg was given daily starting day +5 and continuing until neutrophil engraftment. Standard pneumocystis prophylaxis was started on day +30 and continued at least 6 months post-transplant and until immunosuppression was discontinued. Quantitative cytomegalovirus (CMV) PCR was monitored weekly starting day +1 and pre-emptive therapy initiated if viral reactivation was detected (≥400 copies/mL).

Definitions and Study Endpoints

Primary outcomes analyzed were overall survival (OS), disease-free survival (DFS, survival without evidence of active malignancy after transplantation), relapse/progression of malignancy, NRM, GRFS (survival without grade 3 to 4 acute GVHD, moderate to severe chronic GVHD by National Institutes of Health [NIH] grading, and relapse/progression) [14], CGRFS (survival without relapse or active moderate to severe chronic GVHD by NIH grading, at the time of most recent assessment) [15], and time to systemic IST discontinuation. Acute GVHD was classified as clinically significant (grades 2 to 4) or severe (grades 3 to 4) [16]. Chronic GVHD was classified as mild, moderate, or severe by NIH consensus criteria [17]. Acute and chronic GVHD were evaluated and graded by a single practitioner within the program. NRM and relapse were treated as competing risks. Primary and secondary graft failure were considered a single outcome. Primary graft failure was defined as failure to achieve an ANC of $\geq 0.5 \times 10^9$/L for 3 consecutive days or donor chimerism <5%. Secondary graft failure was defined as initial donor engraftment followed by graft loss, evidenced by a persistent decline in the absolute neutrophil account (ANC) (<0.5 × 109/L) or loss of donor chimerism <5% or a second transplant in patients with documented clinical remission [18].

Statistical Methods

Cumulative incidences of NRM, relapse, acute GVHD, chronic GVHD, and systemic IST discontinuation were computed to accommodate competing risks [19]. Probabilities of OS, DFS, and GRFS were estimated using the Kaplan-Meier method. Generation of the CGRFS curve was accomplished by linear combination of 5 Kaplan-Meier estimates to accommodate 2 episodes of chronic GVHD onset and resolution [15]. Survival functions and cumulative incidences were compared between the disease risk index (DRI) subgroups [20] and GVHD subgroups using the log-rank and Gray's test, respectively. We performed landmark analyses for GVHD events. One year and 6 months were chosen to be the landmarks for moderate to severe chronic GVHD and grade 3 to 4 acute GVHD, respectively. Patients who died within the landmark were excluded for OS estimation. Patients who died or relapsed within the landmark were excluded for estimation of DFS, NRM, and relapse. A survival outcome was determined to be significantly different between these 2 groups if the observed *P*value was <.05.

RESULTS

Characteristics of the Study Cohort

A total of 82 consecutive patients with a median age of 42 years (range, 19 to 61 years) with high-risk hematologic malignancies were transplanted using this regimen between May 2011 and December 2017. Patient and donor characteristics are listed in Table 1. Transplant diagnosis included AML (n = 42), ALL (n = 27), chronic myelogenous leukemia (n = 5), MDS (n = 3), non-Hodgkin lymphoma (n = 3), or other (n = 2). DRI was classified as low (n = 6),

Table 1
Table of Characteristics (N = 82)

Patient age, median (range)	42 (19, 61)
Male sex	47 (57%)
Race	
White	41 (50%)
Black	40 (49%)
Asian	1 (1%)
Diagnosis	
AML	42 (51%)
ALL	27 (33%)
CML	5 (6%)
MDS	3 (4%)
NHL	3 (4%)
AL	2 (2%)
DRI	
Low	6 (7%)
Intermediate	44 (54%)
High	23 (28%)
Very high	9 (11%)
HCT-CI	
0-2	43 (52%)
≥3	39 (48%)
Patient CMV	
Positive	65 (79%)
Negative	17 (21%)
Donor relation	
Child	29 (35%)
Sib	35 (43%)
Parent	18 (22%)
ABO compatibility	
Compatible	55 (67%)
Incompatible minor	20 (24%)
Incompatible major	6 (7%)
Incompatible minor & major	1 (1%)
Female donor male recipient	16 (20%)
Donor age, median (range)	31 (16, 74)
Donor male sex	50 (61%)
Donor CMV	
Positive	55 (67%)
Negative	27 (33%)
Year of transplantation	
2011-2014	35 (43%)
2015-2017	47 (57%)
# of survivors	56
Survivor follow-up, median (range)	47 (16, 95)

Abbreviations: AML, acute myeloid leukemia; AL, acute leukemia, unspecified; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukmia; CMV, cytomegalovirus; DRI, disease risk index; HCT-CI; hematopoietic cell transplant-specific comorbidity index; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma

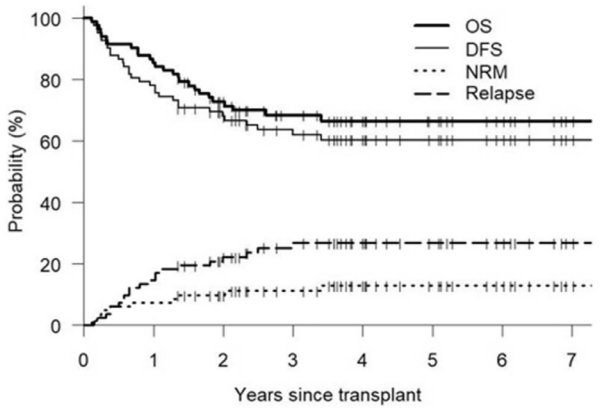

Figure 1. Transplant outcomes: probability of overall and disease-free survival; cumulative incidence of relapse/progression and nonrelapse mortality.

intermediate (n = 44), high (n = 23), and very high (n = 9) risk. Hematopoietic cell transplant-specific comorbidity index was ≥3 in 47%, and recipient CMV seropositivity was 79%. Haploidentical donors were children, siblings/half-siblings, or parents in 35%, 43%, and 22%, respectively. Median (range) donor age was 31 (16 to 74) years. No recipients had a positive flow cytometric HLA crossmatch against their donor before transplant.

Relapse, DFS, and OS

One-year OS, DFS, and cumulative incidence of relapse (CIR) were 85%, 78%, and 15%, respectively. With a median (range) follow-up of 47 (16 to 95) months, estimated 4-year OS, DFS, and CIR were 67%, 60%, and 27%, respectively for all patients (Figure 1). For standard-risk patients (low/intermediate DRI), corresponding values were 77%, 69%, and 20%, respectively, compared with 50%, 47%, and 38% for high-risk patients (high/very high DRI). Four-year DFS was significantly lower in patients with high/very high DRI because of higher relapse risk (Figure 2).

Disease-Specific Subset Analysis

In the subset of patients with AML/MDS (n = 45), estimated 4-year OS, DFS, and CIR were 65%, 61%, and 25%, respectively (low/intermediate-risk DRI 69%, 67%, and 16%; high/very high-risk DRI 59%, 53%, and 41%, respectively) (Supplementary Figure S1A). Four-year CIR was significantly higher in patients with AML/MDS with high/very high DRI because of higher relapse risk, leading to lower DFS (Supplementary Figure S1B). In patients with ALL (n = 27), 4-year OS, DFS, and CIR were 62%, 51%, and 35%, respectively (Supplementary Figure S1C). There were no significant differences in survival or CIR between patients with AML/MDS and ALL (Supplementary Figure S1D).

GVHD, GRFS, CGRFS, and Time to Immunosuppression Discontinuation

The cumulative incidence of grades 2 to 4 and grades 3 to 4 acute GVHD by day +180 was 52% and 17%, respectively. The cumulative incidence of chronic GVHD at 4 years post-transplant was 37% (moderate to severe, 23%; severe, 12%). All cases of chronic GVHD except 1 occurred before 12 months post-transplant. To better assess the impact of clinically significant GVHD (grade 3 to 4 acute or moderate to severe chronic GVHD) on outcome, we performed landmark analyses (at 6 months post-transplant for acute GVHD and 12 months post-transplant for chronic

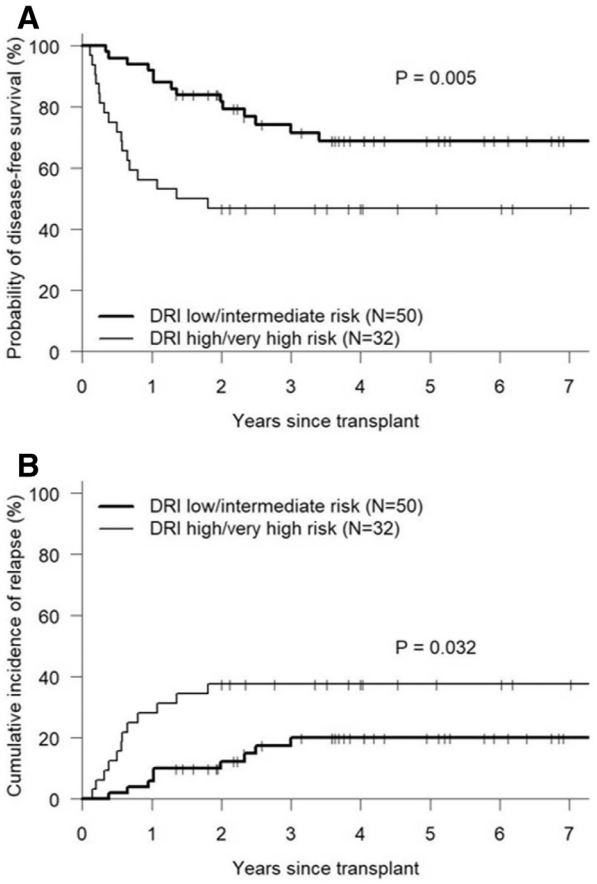

Figure 2. (A) Probability of disease-free survival and (B) cumulative incidence of relapse/progression, according to disease risk index (low/intermediate versus high/very high).

GVHD). Development of moderate to severe chronic GVHD had no effect on survival compared with those without this event (4-year OS 79% versus 78%, $P = .88$; Figure 3A). In contrast, patients developing grade 3 to 4 acute GVHD had inferior survival compared with patients without severe acute GVHD, when landmarked at 6 months (4-year OS 45% versus 79%, $P = .023$; Figure 3B). This was the result of higher NRM in patients experiencing grade 3 to 4 acute GVHD (4-year NRM 40% versus 2%, $P < .001$; Figure 3C).

Median (range) time to discontinuation of systemic IST was 7.8 (2.0 to 39.7) months, with 84% of patients off of all systemic IST by 2 years post-transplant (Figure 4A). CGRFS at 2, 3, and 4 years post-transplant was 60%, 57%, and 60%, respectively (indicating freedom from relapse and need for long-term systemic immunosuppression for GVHD) (Figure 4B). Conventional GRFS at 1 and 4 years post-transplant was 46% and 37%, respectively (Figure 4C).

Engraftment and Chimerism

There were no cases of primary or secondary engraftment failure. Median day (range) to neutrophil and platelet recovery was day +16 (12 to 27) and day +26 (15 to 228), respectively. Achievement of full donor chimerism was rapid with all evaluable patients achieving durable complete (>95%) donor T cell and myeloid chimerism by day +30.

Post-Transplant Fever, Infection, and NRM

Fever occurred in the first 4 days post-transplant in all but 1 patient. The median maximum temperature was 39.4°C

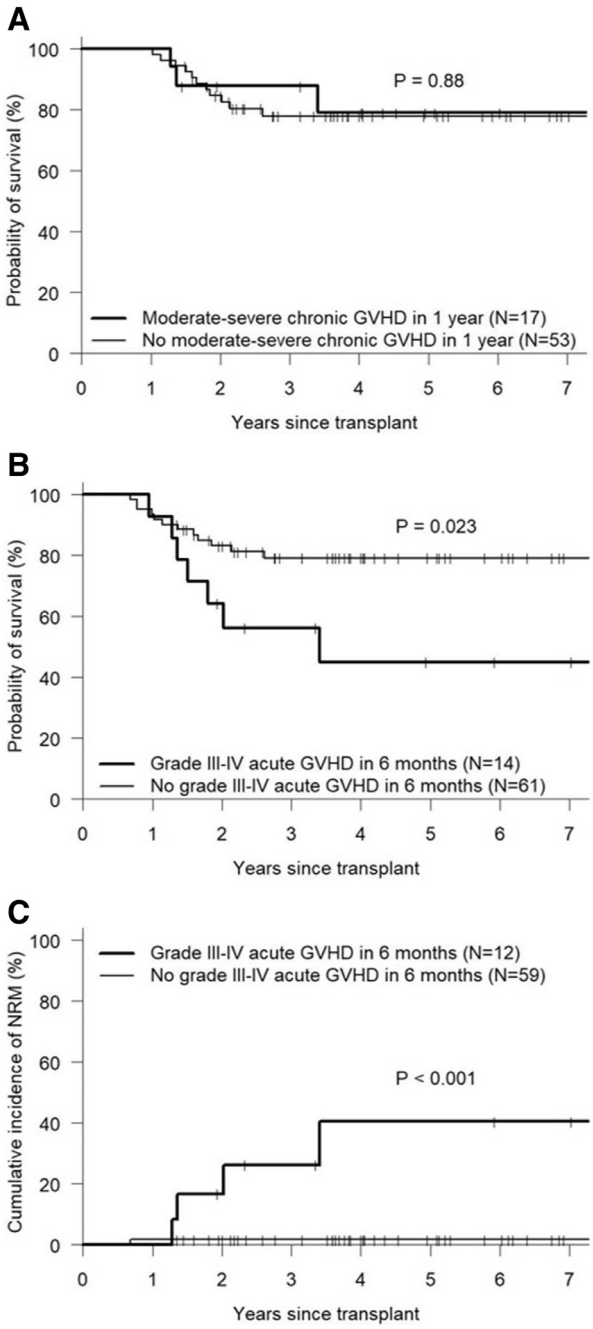

Figure 3. (A) Probability of overall survival in patients stratified by occurrence of moderate to severe chronic GVHD: landmark analysis at 12 months. (B) Probability of overall survival in patients stratified by occurrence of grade 3 to 4 acute GVHD: landmark analysis at 6 months. (C) cumulative incidence of nonrelapse mortality in patients stratified by occurrence of grade 3 to 4 acute GVHD: landmark analysis at 6 months.

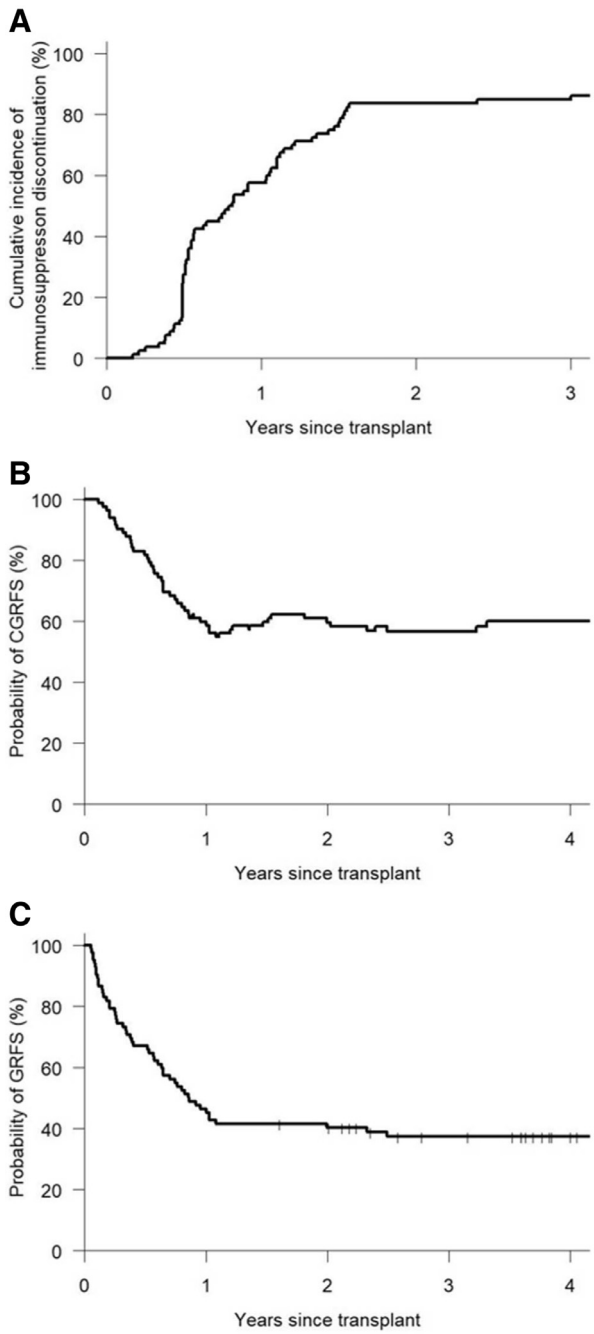

Figure 4. (A) Cumulative incidence of systemic immunosuppression discontinuation; probability of (B) current GRFS and (C) conventionally defined GRFS.

(range, 38.1 to 40.7°C). Median time to first fever and maximum temperature was day +1 (range, 0 to +4) and day +3 (range, 0 to +4), respectively. No patient experienced grade ≥2 cytokine release syndrome, defined by the need for supplemental oxygen or intervention-requiring hypotension [21] in the first 7 days post-transplant.

CMV reactivation, requiring antiviral therapy, occurred in 54% of patients with a median time to CMV reactivation of day +32 days. CMV disease was seen in 2% of patients. Grade 1/2 BK virus cystitis was seen in 38% of patients, with severe manifestations (≥ grade 3) in only 2%. There were no cases of Epstein-Barr virus lymphoproliferative disease. NRM at 1 and 4 years was 7% and 13%, respectively. Causes of death are reported in Table 2.

DISCUSSION

In this report, we describe the long-term outcome results of 82 consecutive adult patients receiving MAC HIDT following a uniform protocol of fludarabine/TBI 1200 cGy conditioning, PBSC graft, PTCy, tacrolimus, and mycophenolate mofetil. Consistent with the results of our initial pilot study, universal engraftment, low rates of NRM and clinically significant GVHD,

Table 2
Causes of Death (n = 26)

Relapse/progression	16 (62%)
AML	9
ALL	6
CML-BC	1
Organ Failure	5 (19%)
ARDS	1
DAH	1
SCD	1
Hepatic SOS	1
MOF	1
Infection	3 (11%)
PNA (fungal)	2
PNA (bacterial)	1
GVHD	2 (8%)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ARDS, acute respiratory distress syndrome; CML-BC, chronic myelogenous leukmia, blast crisis; DAH, diffuse alveolar hemorrhage; GVHD, graft-versus-host disease; MOF, multiorgan failure; PNA, pneumonia; SCD, sudden cardiac death; SOS, sinusoidal obstruction syndrome.

and favorable relapse rates were again demonstrated in this much larger cohort with significantly longer follow-up time. Long-term DFS was achieved in approximately 70% of low/intermediate DRI patients and half of those with high/very high DRI. In addition, this study extends our initial findings with new analyses evaluating the burden of ongoing GVHD and the need for systemic IST. We show that by 2 years post-transplant, 84% of patients have discontinued IST and that 60% of patients are alive, in remission, off systemic IST, and free of active GVHD.

Our analysis confirms previously published data that MAC can be applied safely to younger patients receiving HIDT-PTCy without excessive toxicity. In fact, the 1-year NRM of 7% in this study appears no higher than the 11% 1-year NRM described with the original "Baltimore" nonmyeloablative regimen, while 3-year relapse rates appear lower (25% versus 46% overall, 38% versus 67% in high/very high DRI patients) [8]. Remarkably for a HIDT regimen, there were no incidences of primary or secondary engraftment failure. Last, the incidence of clinically significant infectious complications was low (2% CMV disease, 2% severe BK cystitis, and no cases of Epstein-Barr virus lymphoproliferative disease (LPD)).

When compared with a previously published large registry study by the Center for International Blood and Marrow Transplant Research (CIBMTR) evaluating the role of graft source, peripheral blood versus marrow, for HIDT-PTCy [22], rates of grade 3 to 4 acute GVHD (17% versus 10%) and moderate to severe chronic GVHD (23% versus 17%) in the current study may be slightly higher than those in the peripheral blood cohort in the registry study. Despite this, any increase in clinically significant GVHD was not reflected in NRM (13% versus 16%). Although the results of our landmark analysis did not show any significant effect of moderate to severe chronic GVHD on transplant outcome, it did demonstrate a detrimental effect of grade 3 to 4 acute GVHD on both NRM and survival. In this regard, further efforts to decrease the risk of severe acute GVHD are warranted.

Although MAC regimens are routinely used for younger and more physically fit patients undergoing matched related or unrelated allogeneic transplantation for hematologic malignancy, HIDT-PTCy has relied on RIC until recently. A recently completed CIBMTR registry study, presented at the 2018 American Society of Hematology meeting, demonstrated improved DFS for patients <55 years of age receiving MAC versus RIC HIDT-PTCy, after controlling for the effect of other significant covariates, including hematopoietic cell transplant-specific comorbidity index, disease type, DRI, and stem cell source [23]. The DFS advantage was caused by a significantly lower relapse risk in recipients of MAC without a corresponding increase in NRM. Although these results should be confirmed in the context of a prospective phase III study, they still point to the potential importance of conditioning intensity in younger patients with high-risk hematologic malignancies receiving HIDT.

The optimal preparative regimen for MAC HIDT-PTCy remains an unanswered question, particularly the role of TBI- versus non-TBI-based conditioning. In the abovementioned retrospective CIBMTR analysis, there were no significant differences in survival, NRM, or relapse risk between TBI- and non-TBI-based HIDT-PTCy [23]. However, this does not preclude other important differences outside of survival. Importantly, BK virus-associated hemorrhagic cystitis has been reported to be a source of significant morbidity for HIDT patients. We previously demonstrated that BK virus-associated hemorrhagic cystitis occurs with increased frequency and severity following busulfan- versus TBI-based MAC HIDT-PTCy [24]. Here we confirm the relatively low frequency and severity of this complication following this TBI-based MAC regimen for HIDT in a larger patient population with prolonged follow-up. However, other complications of a TBI-based regimen may need to be balanced against these observed benefits. For example, some studies suggest higher rates of late second malignancies in patients receiving TBI for conditioning, particularly in younger adults [25].

The experience of 82 consecutive patients with long-term follow-up reported here suggests that fludarabine/TBI-based MAC HIDT-PTCy is a promising alternative for patients ≤60 years with advanced hematologic malignancies who lack timely access to a matched related or unrelated donor. The low risk of engraftment failure, infectious complications, and severe GVHD translated into a relatively low long-term incidence of NRM. Furthermore, this fact combined with a relatively low rate of disease relapse resulted in excellent long-term OS (67%) at 4 years for all patients and 77% for standard risk (low/intermediate DRI) patients. Although 4-year OS of 50% in high/very high-risk DRI patients was acceptable in comparison to other reports [8], relapse of malignancy remains an important challenge in this group for further investigation.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.06.017.

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