Risk Factors for Graft-versus-Host Disease in Haploidentical Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide

A full list of authors and affiliations appears at the end of the article.

Abstract

Post-transplant cyclophosphamide (PTCy) has significantly increased the successful use of haploidentical donors with relatively low incidence of GVHD. Given its increasing use, we sought to determine risk factors for GVHD after haploidentical hematopoietic cell transplantation (haploHCT) using PTCy.

Data from the Center for International Blood and Marrow Transplant Research on adult patients with AML, ALL, MDS, or CML who underwent PTCy-based haploHCT (2013–2016) were analyzed and categorized into 4 groups based on myeloablative (MA) or reduced intensity (RIC) conditioning and bone marrow (BM) or peripheral blood (PB) graft source.

646 patients were identified (MA-BM = 79, MA-PB = 183, RIC-BM = 192, RIC-PB = 192). The incidence of grade 2–4 aGVHD at 6 months was highest in MA-PB (44%), followed by RIC-PB (36%), MA-BM (36%), and RIC-BM (30%) (p=0.002). The incidence of chronic GVHD at 1 year was 40%, 34%, 24%, and 20%, respectively (p<0.001). In multivariable analysis, there was no impact of stem cell source or conditioning regimen on grade 2–4 acute GVHD; however, older donor age (30–49 versus <29 years) was significantly associated with higher rates of grade 2–4 acute GVHD (HR 1.53, 95% CI 1.11–2.12, p=0.01). In contrast, PB compared to BM as a stem cell source was a significant risk factor for the development of chronic GVHD (HR 1.70, 95% CI 1.11–2.62, p=0.01) in the RIC setting. There were no differences in relapse or overall survival between groups.

Donor age and graft source are risk factors for acute and chronic GVHD, respectively, after PTCy-based haploHCT. Our results indicate that in RIC haploHCT, the risk of chronic GVHD is higher with PB stem cells, without any difference in relapse or overall survival.

Corresponding Author: Betty Ky Hamilton, MD, Blood and Marrow Transplant Program, Taussig Cancer Institute, Cleveland Clinic, 9500 Euclid Avenue CA 60, Cleveland, OH 44195, Phone: (216)-445-7580, Fax: (216)-444-9464, hamiltb2@ccf.org.
*These authors contributed equally to this manuscript

Introduction

For adults with advanced hematologic malignancies, haploidentical donors allow patients without a matched related or unrelated donor the opportunity to proceed with a potentially curative allogeneic hematopoietic cell transplant (HCT).(1–3) The use of post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis has significantly improved outcomes for haploidentical HCT, approaching those in the matched related and unrelated donor setting.(4, 5) Studies evaluating T-cell replete haploidentical HCT using PTCy have demonstrated rates of acute GVHD in the range of 14–41% and chronic GVHD rates of 0–31%, compared to historical rates of 20–80% and 30–70%, respectively, in matched related and matched unrelated donor transplants.(6–8) The majority of these haplo-transplants were done using reduced-intensity conditioning (RIC) regimens with bone marrow (BM) as a graft source.(3–5, 9–21)

Peripheral blood (PB) grafts have also been increasingly used in the haploidentical setting, and there have been two retrospective analyses comparing BM and PB. A small study by O'Donnell et al., demonstrated no differences in acute GVHD at 100 days, chronic GVHD at 2 years, or OS at 2 years between BM (33%, 23%, 58%, respectively) and PB (40%, 19%, 66%, respectively). However, the rate of relapse was higher with BM compared to PB (19% vs 49%).(14) In contrast, a large CIBMTR analysis by Bashey et al. demonstrated a significantly lower incidence of grades II-IV acute GVHD (HR 0.45, p<0.001) and chronic GVHD (HR 0.35, p<0.001) in BM compared to PB.(9) Relapse was also higher with BM compared to PB (HR 1.49, p=0.009) specifically in patients with leukemia, however there were no differences in OS or non-relapse mortality (NRM).

Although the incidences of GVHD after haploidentical HCT have been described, there is little data describing risk factors for GVHD in this setting. The aim of this study is to describe the incidence, characteristics, and risk factors for acute and chronic GVHD in adult patients with hematologic malignancies who underwent a PTCy-based haploidentical HCT from 2013–2016.

Materials and Methods

Data Source

This was a retrospective analysis using data from the CIBMTR. The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 420 transplantation centers worldwide that contribute data on consecutive allogeneic and autologous HCTs to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the capacity of the CIBMTR as a public health authority under HIPPAA regulations. The CIBMTR collects data at two levels, Transplant-Essential Data (TED) and Comprehensive Report Form (CRF). The TED level data is an internationally accepted standard of data that contains key variables for all consecutive

transplant recipients in the United States. When a transplant is registered with the CIBMTR, a subset of patients are selected for the CRF level of data collection. The CRF level data capture additional data related to the patient, disease, and transplant. Thus, a greater number of patients contribute to TED level data compared to CRF data. Additional details regarding the CIBMTR registry have been previously described.(22)

Patients

Eligible patients were 18 years with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS). All patients underwent HCT from a haploidentical donor (defined in the CIBMTR registry as 1 or more antigen-level mismatch among HLA-A, -B, -C, and –DRB1) using BM or PB as a graft source and GVHD prophylaxis with PTCy, tacrolimus, and mycophenolate mofetil; other PTCy-based prophylaxis regimens were excluded to limit heterogeneity and due to low numbers of these regimens. Conditioning regimens included myeloablative (MAC) or RIC, with or without total body irradiation (TBI).(23, 24) An RIC regimen was defined as a) TBI does of 500 cGy as a single fraction or 800 cGy if fractionated, b) <9 mg/kg of oral busulfan or intravenous equivalent, or c) <140 mg/m^2 of melphalan. Transplants using ex-vivo T-cell depletion, antithymocyte globulin (ATG), or alemtuzumab were excluded.

Study Endpoints and definitions

The primary endpoints of this study were incidence of grade II-IV acute GVHD and chronic GVHD. Secondary endpoints included grade III-IV acute GVHD, relapse, OS, non-relapse mortality (NRM), as well as the composite endpoints of GVHD-relapse-free survival (GRFS) (including survival without grade 3–4 acute GVHD, chronic GVHD requiring systemic treatment, relapse or death); and chronic-GVHD relapse-free survival (CRFS) (including survival without chronic GVHD requiring systemic treatment, relapse or death). (25) GVHD was graded according to consensus criteria.(7, 26, 27) Disease status was categorized into early, intermediate, and advanced(28), and the revised Disease Risk Index (DRI) was used to categorize patients into low, intermediate, and high/very high groups.(29) Relapse was defined by hematologic criteria by submitting centers with non-relapse mortality as a competing event. NRM was defined as death without evidence of disease recurrence, relapse was considered a competing event. For relapse, and NRM, patients alive in continuous complete remission were censored at last follow-up. For GVHD, death without the event was considered a competing event. HLA matching was defined as described previously.(30)

Statistical methods

Patient, disease, and transplant-related variables for donor types were compared using chi-square statistics for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate analysis with Gray's test and log-rank test was used for cumulative incidence and survival, respectively. Variables tested included: patient and gender, Karnofsky performance score, hematopoietic cell transplantation comorbidity index (HCT-CI)(31), DRI, time from diagnosis to HCT, donor age and relation (parent, offspring, sibling), donor/recipient gender, donor/recipient CMV status, use of TBI, and year of

transplant. Patients were categorized into 4 groups based on conditioning intensity (myeloablative or reduced intensity) and graft source (bone marrow or peripheral blood). Graft source and conditioning intensity were included in all models. The primary comparisons were RIC-BM versus RIC-PB, and MAC-BM versus MAC-PB.

Multivariable models were built using the Cox's proportional hazards model. All variables were tested to affirm the assumption of proportional hazards and no variables violated the proportional hazards assumption. A stepwise model building procedure was used to select the adjusted factors for each outcome with a threshold of 0.05 for both entry and stay in the model. The 'center' effect was adjusted for all endpoints. Two-way interactions between 'donor type' and the adjusted clinical variables in the models were tested, and no significant interactions were detected. A threshold p-value 0.05 for the primary endpoint of chronic GVHD, and of 0.01 otherwise was used for significance of the main testing variable. A threshold of p-value 0.01/2=0.005 (or 0.05/2=0.025 for the primary endpoint of chronic GVHD) was recommended for the significance of pairwise comparisons when the main variable is significant. The impact of cGVHD on relapse was analyzed by treating cGVHD as a time-dependent covariate in the model for relapse. Results were expressed as a hazard ratio with 95% confidence intervals. SAS software version 9.4 (SAS Institute, Cary, NC) was used in the analysis.

Results

Patients, disease and transplant characteristics

Table 1 shows the characteristics of the study population (N=646) grouped by graft source and conditioning intensity. As expected, the median age of patients undergoing MAC conditioning (45 and 42 years for MAC-BM and MAC-PB, respectively) was younger than those undergoing RIC (60 and 62 years for RIC-BM and RIC-PB, respectively). More patients receiving PB grafts had a higher HCT-CI (score 3) than those receiving BM: (52% MAC-PB compared to 43% MAC-BM, and 62% RIC-PB compared to 42% RIC-BM). Likewise, more patients with a low HCT-CI (score 0) received BM (25% MAC-BM compared to 12% MAC-PB and 24% RIC-BM compared to 14% RIC-PB). As expected, patients receiving PB had overall higher CD34 and CD3 cell doses compared to BM. 47% in the MAC groups received TBI as part of conditioning, with a median dose of 1200 (range 550–1350) while 89% in the RIC groups received TBI, median dose 200 (range 200–400). Median follow-up was longer in the RIC groups compared to the MAC groups: 24 (range 2–53) and 21 (range 6–50) months in RIC-BM and RIC-PB, respectively, versus 13 (range 4–49) and 14 (range 6–50) months in MAC-BM and MAC-PB, respectively.

GVHD and Engraftment

In univariate analysis, the incidence of grade 2–4 acute GVHD at 100 days was highest in MAC-PB at 46% (95% CI 39–54), followed by RIC-PB at 36% (95% CI 29–43), MAC-BM at 33% (95% CI 23–44), and RIC-BM at 27% (95% CI 21–33) (p=0.002). A similar pattern was observed for chronic GVHD, where the incidence at 1 year was highest in MAC-PB at 40% (95% CI 32–47), followed by RIC-PB at 34% (95% CI 27–41), MAC-BM at 24% (95% CI 15–35) and RIC-BM at 20% (95% CI 14–26) (p<0.001) (Table 2).

In multivariable analysis, there were no significant difference in grade 2–4 acute GVHD or grade 3–4 acute GVHD between conditioning and graft source groups (Table 3). Adjusted cumulative incidence of grade 2–4 acute GVHD between all four conditioning and graft source groups is shown in Figure 1. The only significant factor for grade 2–4 acute GVHD in multivariable analysis was donor age 30–49 versus <29 years (HR 1.53, 95% CI 1.11–2.12, p=0.01). For grade 3–4 acute GVHD, older donor age was also the only significant factor (50 versus <29 years, HR 3.89, 95% CI 1.81–8.35, p=0.0005). Despite the impact of donor age, donor relation was not a significant factor for acute GVHD. There was a significantly higher risk for chronic GVHD in the RIC-PB group compared to RIC-BM (HR 1.70, 95% CI 1.11–2.62, p=0.01). There was no difference in chronic GVHD between MAC-PB and MAC-BM (Table 3). Adjusted cumulative incidence curves for chronic GVHD are shown in Figure 2. There were also no differences in chronic GVHD severity among any of the groups; overall, 59% were categorized as mild, 28% were moderate, and 13% were severe (Table 4).

To further determine the significance of graft source on chronic GVHD, subset analyses of MAC (N=262) and RIC (N=384) cohorts were performed. This confirmed an increased incidence of chronic GVHD with PB compared to BM in both MAC (HR 1.81,95% CI 1.00–3.28, p=0.05) and RIC (HR 1.72, 95% CI 1.10–2.70, p=0.02) groups, however this only met the predetermined significance level in the RIC group. Due to the known differences in age between MAC and RIC groups, an age-adjusted analysis for chronic GVHD was also performed and demonstrated similar results (data not shown). We further analyzed chronic GVHD in a larger cohort of CIBMTR patients receiving a haplo-identical transplant (N=1401) using TED level data, and confirmed that in the RIC setting, PB was associated with higher rates of chronic GVHD (p=0.0015). (Table 5).

Regarding hematopoietic recovery, neutrophil recovery at 28 days was highest in MAC-PB (95%), followed by RIC-BM (94%), RIC-PB (93%), and MAC-BM (92%) (p=0.004). Time to neutrophil recovery was comparable across the groups:19 days in MAC-BM (range 5–125), 16 days in MAC-PB (range 1–90), 18 days in RIC-BM (range 2–48), and 17 days in RIC-PB (range 1–105). There was no difference in platelet recovery at 100 days between groups (Table 2). Given the small numbers, there was no notable trend regarding graft failure: 6 in RIC-PB, 4 in RIC-BM, 4 in MAC-PB, and 1 in MAC-BM.

Relapse and Survival Outcomes

Relapse at 1 year was similar among the groups (Table 2, adjusted cumulative incidence shown in Figure 3). In multivariable analysis, revised DRI high/very high versus low (HR 2.11, 95% CI 1.21–3.68, p=0.008) was the only significant factor for relapse. We further analyzed the impact of chronic GVHD on relapse, and found no significant associations between chronic GVHD and relapse in the entire cohort (HR 1.00, 95% CI 0.70–1.44, p=0.99); nor in subset analysis of MA (p=0.80) and RIC (p=0.75) cohorts.

NRM at 1 year was highest in RIC-PB at 18% (95% CI 13–24) and MAC-PB at 18% (95% CI 12–24%), followed by 14% (95% CI 7–23) in MAC-BM, and 9% (95% CI 5–13) in RIC-BM (p=0.01) (Table 2). In multivariable analysis, there was a higher risk of NRM in RIC-PB compared to RIC-BM (HR 2.06, 95% CI 1.15–3.68, p=0.01). There was no difference in

NRM between MAC-PB and MAC-BM. Adjusted cumulative incidence of NRM between groups (p=0.0292) is shown in Figure 4. The other significant factors for NRM were older patient age 60 versus 18–29 years (HR 2.31, 95% CI 1.18–4.54, p=0.015) and higher HCT-CI 3 versus 0 (HR 3.32, 95% CI 1.50–7.35, p=0.003).

GRFS and CRFS at 1 year were lowest in the PB groups for both RIC (25% and 26% respectively, compared to 41 and 43% in BM groups) and MAC (23% and 26%, compared to 38% and 42%) (Table 2), but in multivariable analysis, these outcomes were not significantly impacted by graft source or conditioning regimen (adjusted probability, Figure 5). Donor age 50 versus <29 years (HR 1.43, 95% CI 1.08–1.88, p=0.012) and Karnofsky performance score 90–100 versus <90 (HR 0.74, 95% CI 0.61–0.90, p=0.003) were significant factors for GRFS, whereas patient age 50–59 versus 18–29 years (HR 1.53, 95% CI 1.09–1.96, p=0.013) and patient race Non-Caucasian versus Caucasian (HR 1.33, 95% CI 1.07–1.65, p=0.010) were significant factors for CRFS.

OS at 1 year in univariate analysis was similar among all groups (Table 2). In multivariable analysis, patient age 50–59 (HR 1.73, 95% CI 1.12–2.68, p=0.013) or 60 years (HR 1.84, 95% CI 1.20–2.82, p=0.005) versus 18–29 years, donor age 50 versus <29 years (HR 1.77, 95% CI 1.24–2.52, p=0.002), and revised DRI high/very high versus low (HR 2.68, 95% CI 1.46–4.90, p=0.001) were significant factors contributing to OS. Relapse was the leading cause of death in all groups (Table 6).

Discussion

This study demonstrates that donor age and graft source are important risk factors for acute and chronic GVHD, respectively, after PTCy-based haploidentical HCT. Similar to previous findings in both matched (32–34) and alternative (35) donor settings, PB grafts in RIC haplo-transplant were found to be significantly associated with chronic GVHD of any severity. Although the impact of specific components of transplant are historically studied as distinct entities (36), we report a significant association of graft source and conditioning (RIC-PB) on chronic GVHD.

Previous studies have reported incidences of acute and chronic GVHD after PTCy-based haploidentical HCT with varying combinations of stem cell sources and conditioning regimens, but only 2 prior studies have compared BM and PB grafts. O'Donnell et al. reported no difference in GVHD or OS but lower relapse with PB, whereas Bashey et al. demonstrated higher incidences of acute and chronic GVHD, as well as lower relapse with PB without a difference in OS.(9, 14) Our study confirms the finding of increased chronic GVHD with PB grafts, however, only in the reduced intensity conditioning setting. Despite the incidence of chronic GVHD at 1 years being highest in the MAC-PB cohort, there was no difference confirmed in multivariable analysis in the myeloablative setting. While GRFS and CGFRS were inferior in the PB groups in both RIC and MAC groups, there was no difference in risk of relapse or overall survival between any of the groups. These results suggest that PTCy does not fully negate the risk of chronic GVHD using PB in the RIC setting. Moreover, no other factors emerged as significant risk factors for development of chronic GVHD after haploidentical HCT with PTCy. Notably, the higher risk of chronic

GVHD with the use of PB was not offset by a lower relapse rate nor difference in overall survival. The ability to detect these differences in relapse and survival is likely to be limited by power. There was also no increase in graft failure with BM compared to PB grafts, with a similar time to neutrophil engraftment in all groups.

The effect of both graft source and conditioning was also confirmed in our analyses of a larger cohort of CIBMTR patients using TED level data receiving haplo-transplant. Thus although conditioning intensity is usually determined by a patient's age, co-morbidities and other non-modifiable factors, graft source is a potentially modifiable variable.

It is also notable that overall incidence of grade 3–4 acute GVHD was low, especially in the RIC setting, a similar finding to what has been recently reported by McCurdy et al. suggesting that PTCy immunomodulation decreases the risk of severe acute GVHD without reduction of grade 2 GVHD, which was significantly associated with higher progression-free survival.(37) In contrast to this recent analysis, we demonstrate older donor age as a significant risk factor for both grade 2–4 and grade 3–4 acute GVHD, as opposed to donor relation which did not have an impact. We were unable to evaluate cell doses for this analysis. Of note, the distribution of donor age between RIC and MAC were similar. This may have implications on donor selection when there is more than one haploidentical donor available (e.g. older sibling versus younger offspring). Other studies have also shown donor age to be a factor in outcomes after haploidentical transplant, and our findings support this as a recommended consideration in donor selection.(38–40)

There are several limitations that should be considered in interpreting these results. First, this was a retrospective analysis based on data submitted to a registry, and thus factors that led to decisions regarding stem cell source and conditioning regimen cannot be determined. We did restrict the analysis to select conditioning and prophylaxis regimens to limit heterogeneity. In addition, although the use of the registry data allowed for a large study population, it is possible that we did not have the power to elicit other risk factors contributing to GVHD, or significant relationships in the observed trends. The power to detect significant differences in chronic GVHD in our subset analysis of MAC and RIC groups was just 48% and 66%, respectively, and this may be why we were unable to detect significant differences in graft source in the MAC setting for GVHD. Nevertheless, our findings of increased chronic GVHD in the RIC groups were further confirmed by a larger cohort using TED level data. This was one of the largest analyses of this type, allowing the ability to evaluate conditioning regimen and graft source as specific risk factors for GVHD after haploidentical HCT. Another limitation includes the duration of follow up for the MAC groups, which were only 13 and 14 months, compared to the RIC groups who had 24 and 21 months of follow up. Notably, the follow up was similar between the BM and the PB groups, thus the subset analyses within the MAC and the RIC groups were not impacted by different follow up periods. Although most relapse and chronic GVHD occur within 1 year of transplant, longer follow up particularly in the MAC groups are necessary, especially given that there was not a difference in chronic GVHD between the MAC groups. In addition, we excluded patients (N=24) who received in-vivo T-cell depletion with ATG or alemtuzumab, as it is known that these agents decrease the incidence of chronic GVHD.(41, 42) Patients who received both PTCy and in-vivo T-cell depletion may potentially have had lower risks

of chronic GVHD, although this was overall a small number of patients. Finally, we included only patients with AML, ALL, CML, and MDS, and thus our findings are applicable to only this patient population.

In sum, our results show that PB stem cells contribute to an increased risk of chronic GVHD and NRM in RIC PTCy-based haploidentical HCT, and that other outcomes such as relapse and overall survival are similar. These results aid in decision making regarding graft source in RIC PTCy-based haploidentical HCT. Prospective evaluation of PB versus BM using PTCy platforms is needed to confirm these findings.

Authors

Annie Im[1,*], Armin Rashidi[2,*], Tao Wang[3,4], Michael Hemmer[3], Margaret L. MacMillan[5], Joseph Pidala[6], Madan Jagasia[7], Steven Pavletic[8], Navneet S. Majhail[9], Daniel Weisdorf[10], Hisham Abdel-Azim[11], Vaibhav Agrawal[12], A. Samer Al-Homsi[13], Mahmoud Aljurf[14], Medhat Askar[15], Jeffery J. Auletta[16], Asad Bashey[17], Amer Beitinjaneh[18], Vijaya Raj Bhatt[19], Michael Byrne[7], Jean-Yves Cahn[20], Mitchell Cairo[21], Paul Castillo[22], Jan Cerny[23], Saurabh Chhabra[3], Hannah Choe[24], Stefan Ciurea[25], Andrew Daly[26], Miguel Angel Diaz Perez[27], Nosha Farhadfar[28], Shahinaz M. Gadalla[29], Robert Gale[30], Siddhartha Ganguly[31], Usama Gergis[32], Rabi Hanna[33], Peiman Hematti[34], Roger Herzig[35], Gerhard C. Hildebrandt[36], Deepesh P. Lad[37], Catherine Lee[38], Leslie Lehmann[39], Lazaros Lekakis[18], Rammurti T. Kamble[40], Mohamed A. Kharfan-Dabaja[41], Pooja Khandelwal[42,43], Rodrigo Martino[44], Hemant S. Murthy[41], Taiga Nishihori[45], Tracey A. O'Brien[46], Richard F. Olsson[47,48], Sagar S. Patel[49], Miguel-Angel Perales[50], Tim Prestidge[51], Muna Qayed[52], Rizwan Romee[53], Hélène Schoemans[54], Sachiko Seo[55], Akshay Sharma[56], Melhem Solh[57], Roger Strair[58], Takanori Teshima[59], Alvaro Urbano-Ispizua[60], Marjolein Van der Poel[61], Ravi Vij[62], John L. Wagner[63], Basem William[64], Baldeep Wirk[65], Jean A. Yared[66], Steve R. Spellman[67], Mukta Arora[68], Betty K. Hamilton[9,*]

Affiliations

[1]University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA [2]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN [3]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI [4]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI [5]Blood and Marrow Transplant Program, Department of Pediatrics, University of Minnesota, Minneapolis, MN [6]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL [7]Vanderbilt Unviersity Medical Center, Nashville, TN [8]Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute, Bethesda, MD [9]Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio [10]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN [11]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, University of

Southern California Keck School of Medicine, Los Angeles, CA [12]Division of Hematology-Oncology, Indiana University School of Medicine, Indianapolis, IN [13]New York University Langone Medical Center, New York, NY [14]Department of Oncology, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia [15]Department of Pathology and Laboratory Medicine, Baylor University Medical Center, Dallas, TX [16]Blood and Marrow Transplant Program and Host Defense Program, Divisions of Hematology/Oncology/Bone Marrow Transplant and Infectious Diseases, Nationwide Children's Hospital, Columbus, OH [17]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA [18]University of Miami, Miami, FL [19]The Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE [20]Department of Hematology, CHU Grenoble Alpes, Grenoble, France [21]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, New York Medical College, Valhalla, NY [22]UF Health Shands Children's Hospital, Gainesville, FL [23]Division of Hematology/Oncology, Department of Medicine, University of Massachusetts Medical Center, Worcester, MA [24]The Ohio State University Wexner Medical Center, James Comprehensive Cancer Center, Columbus, OH [25]The University of Texas MD Anderson Cancer Center; Houston, TX [26]Tom Baker Cancer Center, Calgary, Alberta, Canada [27]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain [28]Division of Hematology/Oncology, University of Florida College of Medicine, Gainesville, FL [29]Division of Cancer Epidemiology & Genetics, NIH-NCI Clinical Genetics Branch, Rockville, MD [30]Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom [31]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS [32]Thomas Jefferson University, Philadelphia, PA [33]Cleveland Clinic Foundation, Cleveland, OH [34]Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin, Madison, WI [35]University of Kentucky Chandler Medical Center, Louisville, KY [36]Markey Cancer Center, University of Kentucky, Lexington, KY [37]Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, India [38]Utah Blood and Marrow Transplant Program at Huntsman Cancer Institute, University of Utah, Salt Lake City, UT [39]Dana-Farber Cancer Institute/Boston ChildrenÆs Hospital, Boston, MA [40]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX [41]Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL [42]Division of Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center [43]Department of Pediatrics, University of Cincinnati, Cincinnati, OH [44]Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain [45]Department of Blood & Marrow Transplant and Cellular Immunotherapy (BMT CI), Moffitt Cancer Center, Tampa, FL [46]Blood & Marrow Transplant Program, Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia [47]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden [48]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden [49]Blood and Marrow Transplant Program,

University of Utah, Salt Lake City, UT [50]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY [51]Blood and Cancer Centre, Starship Children's Hospital, Auckland, New Zealand [52]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA [53]Dana Farber Cancer Institute, Boston, MA [54]Department of Hematology, University Hospitals Leuven and KU Leuven, Leuven, Belgium [55]Department of Hematology and Oncology, Dokkyo Medical University, Tochigi, Japan [56]Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN [57]The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA [58]Rutgers Cancer Institute of New Jersey, Rutgers University, Brunswick, NJ [59]Hokkaido University Hospital, Sapporo, Japan [60]Department of Hematology, Hospital Clinic, University of Barcelona, IDIBAPS, and Institute of Research Josep Carreras, Barcelona, Spain [61]Maastricht University Medical Center, Maastricht, the Netherlands [62]Division of Hematology and Oncology, Washington University School of Medicine, St. Louis, MO [63]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA [64]Division of Hematology, The Ohio State University, Columbus, OH [65]Penn State Cancer Institute, Bone Marrow Transplant Program, Hershey, PA [66]Blood & Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD [67]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI [68]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota Medical Center, Minneapolis, MN

Acknowledgement

References

1. O'Donnell PV, Luznik L, Jones RJ, Vogelsang GB, Leffell MS, Phelps M, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2002;8(7):377–86.

2. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignances using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(6):641–50. doi: 10.1016/j.bbmt.2008.03.005.

3. Brunstein CG, Fuchs EJ, Carter SL, Karanes C, Costa LJ, Wu J, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood. 2011;118(2):282–8. doi: 10.1182/blood-2011-03-344853. [PubMed: 21527516]

4. Bashey A, Zhang X, Sizemore CA, Manion K, Brown S, Holland HK, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignances using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(10):1310–6. doi: 10.1200/JCO.2012.44.3523. [PubMed: 23423745]

5. Ciurea SO, Zhang MJ, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitawi OS, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015;126(8):1033–40. doi: 10.1182/blood-2015-04-639831. [PubMed: 26130705]

6. Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012;18(8):1150–63. doi: 10.1016/j.bbmt.2012.04.005.

7. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(3):389–401 e1. doi: 10.1016/j.bbmt.2014.12.001.

8. Zeiser R, Blazar BR. Pathophysiology of Chronic Graft-versus-Host Disease and Therapeutic Targets. The New England journal of medicine. 2017;377(26):2565–79. doi: 10.1056/NEJMra1703472. [PubMed: 29281578]

9. Bashey A, Zhang MJ, McCurdy SR, St Martin A, Argall T, Anasetti C, et al. Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell-Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(26):3002–9. doi: 10.1200/JCO.2017.72.8428. [PubMed: 28644773]

10. Castagna L, Crocchiolo R, Furst S, Bramanti S, El Cheikh J, Sarina B, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2014;20(5):724–9. doi: 10.1016/j.bbmt.2014.02.001.

11. Di Stasi A, Milton DR, Poon LM, Hamdi A, Rondon G, Chen J, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. Biology of blood

and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2014;20(12):1975–81. doi: 10.1016/j.bbmt.2014.08.013.

12. Kasamon YL, Bolanos-Meade J, Prince GT, Tsai HL, McCurdy SR, Kanakry JA, et al. Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(28):3152–61. doi: 10.1200/JCO.2014.60.4777. [PubMed: 26261255]

13. McCurdy SR, Kanakry JA, Showel MM, Tsai HL, Bolanos-Meade J, Rosner GL, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. Blood. 2015;125(19):3024–31. doi: 10.1182/blood-2015-01-623991. [PubMed: 25814532]

14. O'Donnell PV, Eapen M, Horowitz MM, Logan BR, DiGilio A, Brunstein C, et al. Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: a matched-pair analysis. Bone marrow transplantation. 2016;51(12):1599–601. doi: 10.1038/bmt.2016.215. [PubMed: 27526284]

15. Raiola AM, Dominietto A, di Grazia C, Lamparelli T, Gualandi F, Ibatici A, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2014;20(10):1573–9. doi: 10.1016/j.bbmt.2014.05.029.

16. Blaise D, Furst S, Crocchiolo R, El-Cheikh J, Granata A, Harbi S, et al. Haploidentical T Cell-Replete Transplantation with Post-Transplantation Cyclophosphamide for Patients in or above the Sixth Decade of Age Compared with Allogeneic Hematopoietic Stem Cell Transplantation from an Human Leukocyte Antigen-Matched Related or Unrelated Donor. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(1):119–24. doi: 10.1016/j.bbmt.2015.08.029.

17. Gaballa S, Ge I, El Fakih R, Brammer JE, Kongtim P, Tomuleasa C, et al. Results of a 2-arm, phase 2 clinical trial using post-transplantation cyclophosphamide for the prevention of graft-versus-host disease in haploidentical donor and mismatched unrelated donor hematopoietic stem cell transplantation. Cancer. 2016;122(21):3316–26. doi: 10.1002/cncr.30180. [PubMed: 27404668]

18. Ghosh N, Karmali R, Rocha V, Ahn KW, DiGilio A, Hari PN, et al. Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(26):3141–9. doi: 10.1200/JCO.2015.66.3476. [PubMed: 27269951]

19. Rashidi A, DiPersio JF, Westervelt P, Vij R, Schroeder MA, Cashen AF, et al. Comparison of Outcomes after Peripheral Blood Haploidentical versus Matched Unrelated Donor Allogeneic Hematopoietic Cell Transplantation in Patients with Acute Myeloid Leukemia: A Retrospective Single-Center Review. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(9):1696–701. doi: 10.1016/j.bbmt.2016.05.010.

20. Kanate AS, Mussetti A, Kharfan-Dabaja MA, Ahn KW, DiGilio A, Beitinjaneh A, et al. Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors. Blood. 2016;127(7):938–47. doi: 10.1182/blood-2015-09-671834. [PubMed: 26670632]

21. Bashey A, Zhang X, Jackson K, Brown S, Ridgeway M, Solh M, et al. Comparison of Outcomes of Hematopoietic Cell Transplants from T-Replete Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors: A Multivariable Analysis Including Disease Risk Index. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(1):125–33. doi: 10.1016/j.bbmt.2015.09.002.

22. Horowitz M The role of registries in facilitating clinical research in BMT: examples from the Center for International Blood and Marrow Transplant Research. Bone marrow transplantation. 2008;42 Suppl 1:S1–S2. doi: 10.1038/bmt.2008.101.

23. Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(3):367–9. doi: 10.1016/j.bbmt.2008.12.497.

24. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(12):1628–33. doi: 10.1016/j.bbmt.2009.07.004.

25. Holtan SG, DeFor TE, Lazaryan A, Bejanyan N, Arora M, Brunstein CG, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015;125(8):1333–8. doi: 10.1182/blood-2014-10-609032. [PubMed: 25593335]

26. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone marrow transplantation. 1995;15(6):825–8. [PubMed: 7581076]

27. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. The American journal of medicine. 1980;69(2):204–17. [PubMed: 6996481]

28. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012;120(4):905–13. doi: 10.1182/blood-2012-03-418202. [PubMed: 22709687]

29. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664–71. doi: 10.1182/blood-2014-01-552984. [PubMed: 24744269]

30. Weisdorf D, Spellman S, Haagenson M, Horowitz M, Lee S, Anasetti C, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(7):748–58. doi: 10.1016/j.bbmt.2008.04.003.

31. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9. doi: 10.1182/blood-2005-05-2004. [PubMed: 15994282]

32. Bensinger WI, Martin PJ, Storer B, Clift R, Forman SJ, Negrin R, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. The New England journal of medicine. 2001;344(3):175–81. doi: 10.1056/NEJM200101183440303. [PubMed: 11172139]

33. Flowers ME, Parker PM, Johnston LJ, Matos AV, Storer B, Bensinger WI, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. Blood. 2002;100(2):415–9. doi: 10.1182/blood-2002-01-0011. [PubMed: 12091330]

34. Schmitz N, Eapen M, Horowitz MM, Zhang MJ, Klein JP, Rizzo JD, et al. Long-term outcome of patients given transplants of mobilized blood or bone marrow: A report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. Blood. 2006;108(13):4288–90. doi: 10.1182/blood-2006-05-024042. [PubMed: 16946302]

35. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. The New England journal of medicine. 2012;367(16):1487–96. doi: 10.1056/NEJMoa1203517. [PubMed: 23075175]

36. Jagasia M, Arora M, Flowers ME, Chao NJ, McCarthy PL, Cutler CS, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood. 2012;119(1):296–307. doi: 10.1182/blood-2011-06-364265. [PubMed: 22010102]

37. McCurdy SR, Kanakry CG, Tsai HL, Kasamon YL, Showel MM, Bolanos-Meade J, et al. Grade II Acute Graft-versus-Host Disease and Higher Nucleated Cell Graft Dose Improve Progression-Free Survival after HLA-Haploidentical Transplant with Post-Transplant Cyclophosphamide. Biol Blood Marrow Tr. 2018;24(2):343–52. doi: 10.1016/j.bbmt.2017.10.023.

38. Canaani J, Savani BN, Labopin M, Huang XJ, Ciceri F, Arcese W, et al. Donor age determines outcome in acute leukemia patients over 40 undergoing haploidentical hematopoietic cell transplantation. American journal of hematology. 2018;93(2):246–53. doi: 10.1002/ajh.24963. [PubMed: 29114918]

39. Solomon SR, Sizemore CA, Sanacore M, Zhang X, Brown S, Holland HK, et al. Haploidentical transplantation using T cell replete peripheral blood stem cells and myeloablative conditioning in patients with high-risk hematologic malignancies who lack conventional donors is well tolerated and produces excellent relapse-free survival: results of a prospective phase II trial. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012;18(12):1859–66. doi: 10.1016/j.bbmt.2012.06.019.

40. Karam E, Laporte J, Solomon SR, Morris LE, Zhang X, Holland HK, et al. Who Is a Better Donor for Recipients of Allogeneic Hematopoietic Cell Transplantation: A Young HLA-Mismatched Haploidentical Relative or an Older Fully HLA-Matched Sibling or Unrelated Donor? Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2019. doi: 10.1016/j.bbmt.2019.05.031.

41. Shah AJ, Kapoor N, Crooks GM, Weinberg KI, Azim HA, Killen R, et al. The effects of Campath 1H upon graft-versus-host disease, infection, relapse, and immune reconstitution in recipients of pediatric unrelated transplants. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2007;13(5):584–93. doi: 10.1016/j.bbmt.2007.01.076.

42. Kroger N, Solano C, Wolschke C, Bandini G, Patriarca F, Pini M, et al. Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease. The New England journal of medicine. 2016;374(1):43–53. doi: 10.1056/NEJMoa1506002. [PubMed: 26735993]

Highlights

- In haploidentical HCT with PTCy, conditioning intensity and graft source impact GVHD.

- In RIC, PB compared to BM is significantly associated with chronic GVHD.

- Older donor age was associated with higher risk of acute GVHD and NRM.

Acute GVHD, Grades II-IV
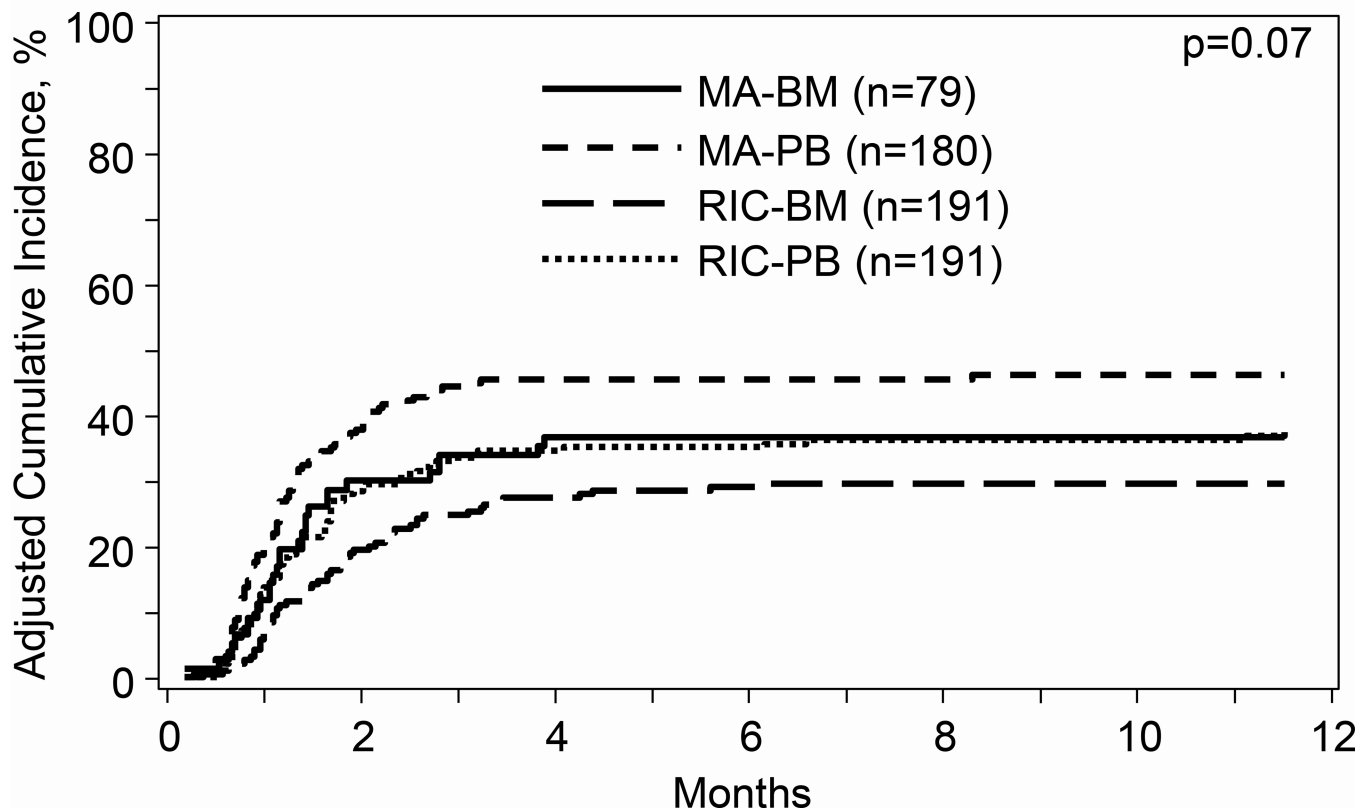
Figure 1.
Incidence of Acute GVHD II-IV by conditioning intensity and graft source.
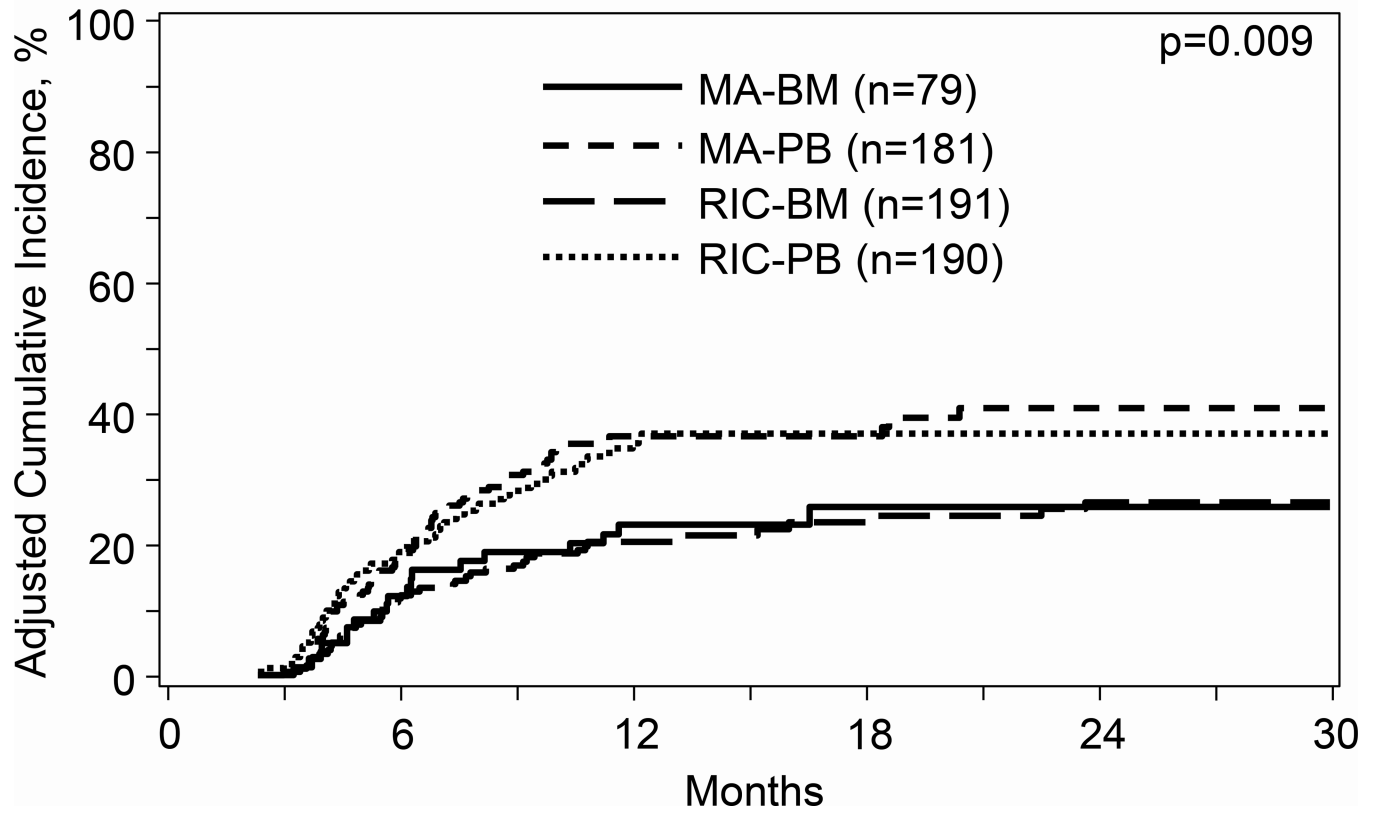
Chronic GVHD

Figure 2.
Incidence of Chronic GVHD by conditioning intensity and graft source.

Relapse
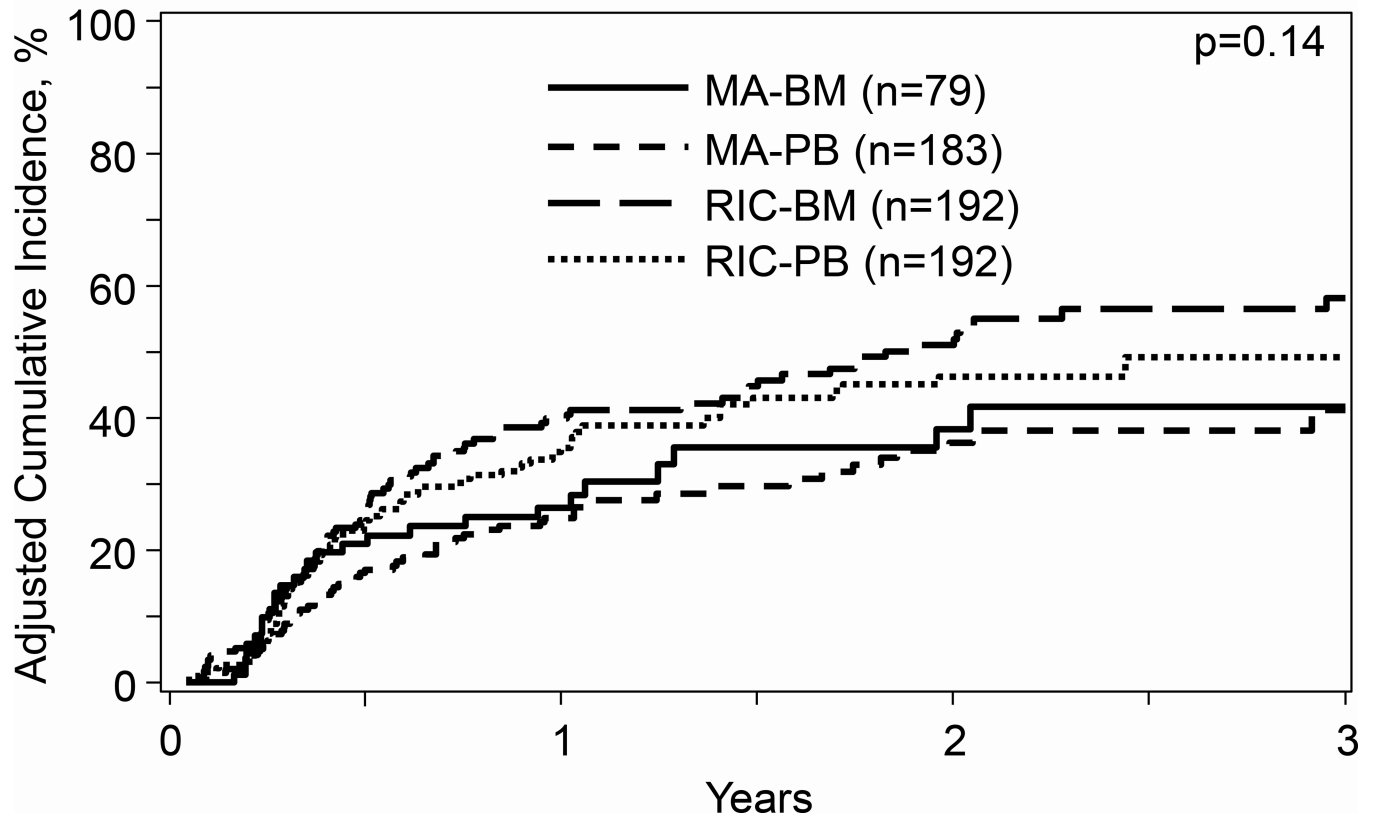
Figure 3.
Incidence of Relapse by conditioning intensity and graft source.

Non-Relapse Mortality

Figure 4.
Incidence of Non-relapse mortality by conditioning intensity and graft source.

GVHD-Free, Relapse-Free Survival

Figure 5.
GVHD-free, relapse free survival by conditioning intensity and graft source.

Table 1.

Baseline characteristics

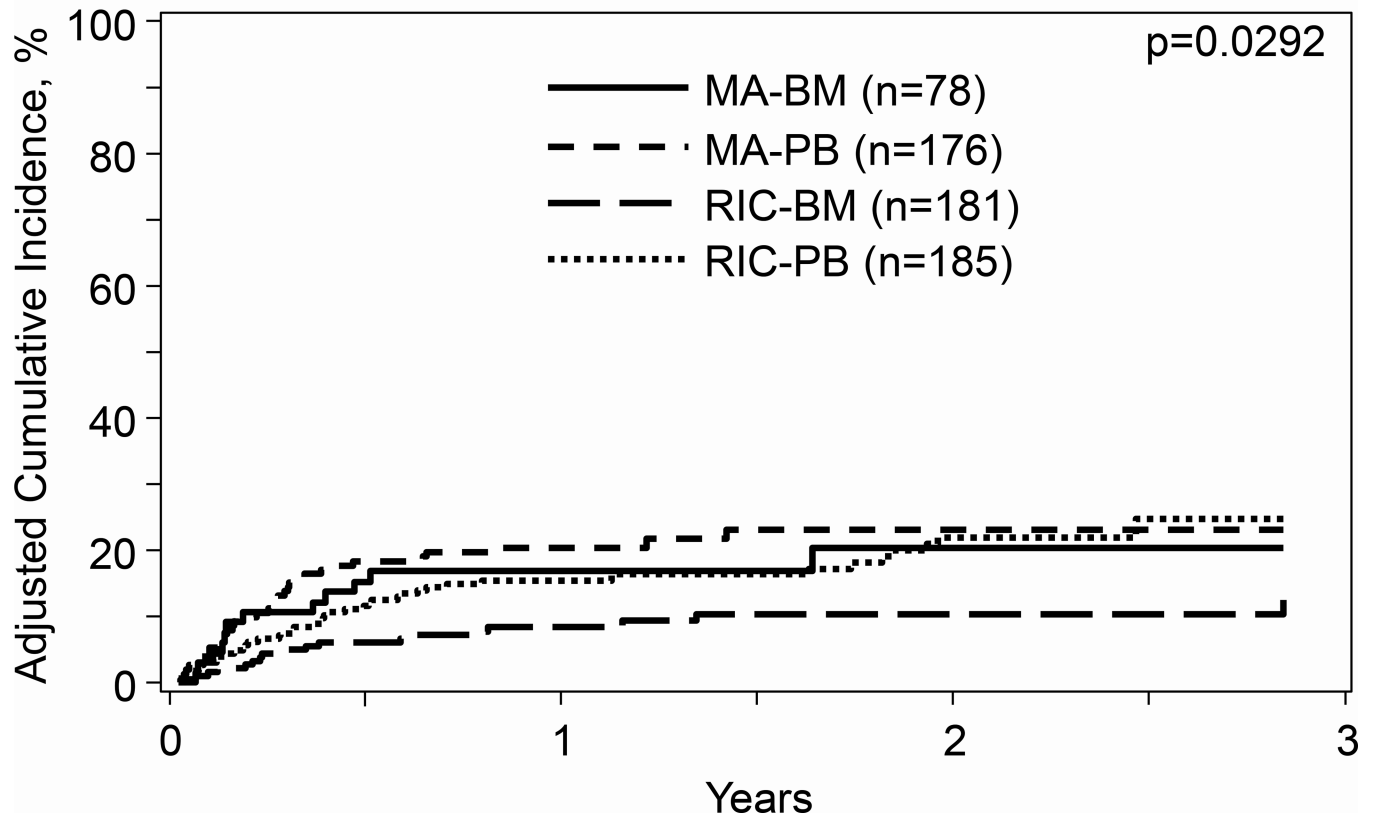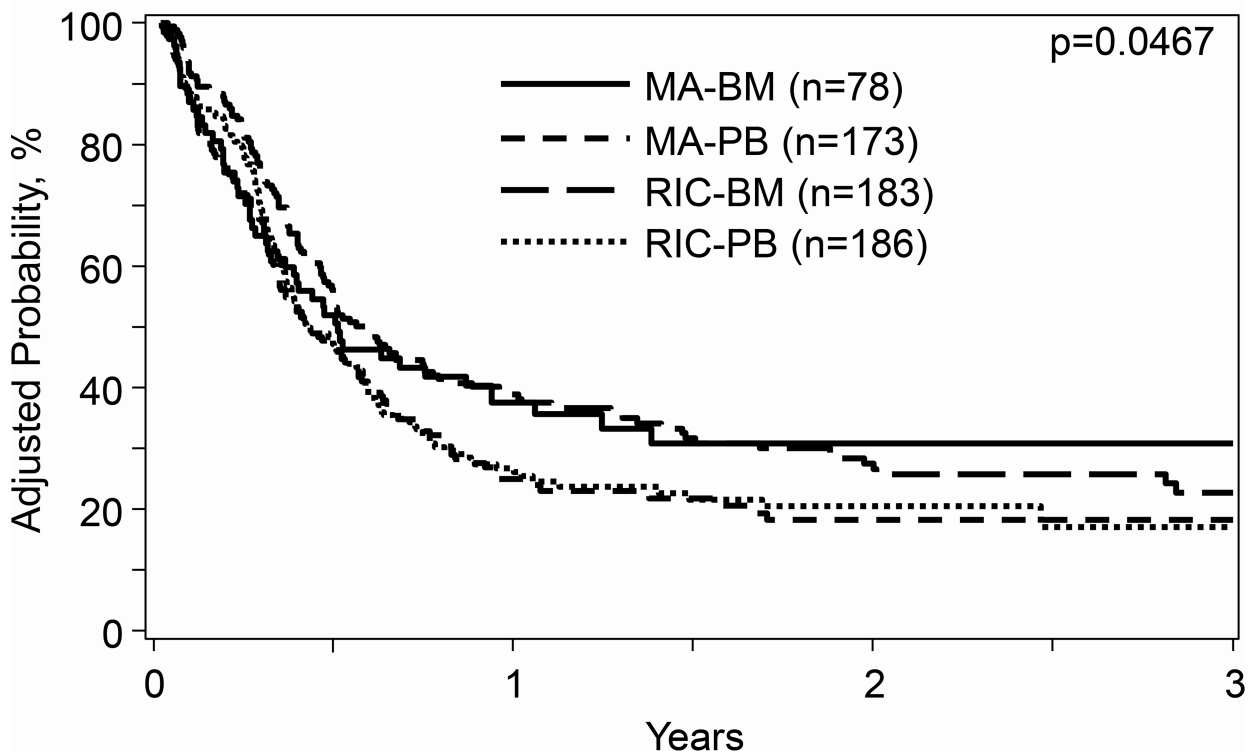| Variable	MAC-BM	MAC-PB	RIC-BM	RIC-PB	P-Value
Number of patients	**79**	**183**	**192**	**192**	
Recipient age at transplant, years					<0.0001[a]
Median (range)	45 (18–72)	42 (18–71)	60 (18–77)	62 (18–76)	<0.0001[b]
18–39	35 (44)	78 (43)	36 (19)	21 (11)	
40–59	24 (30)	77 (42)	56 (29)	55 (28)	
60+	20 (26)	28 (16)	100 (52)	116 (60)	
Recipient gender					0.82[b]
Male	46 (58)	108 (59)	121 (63)	114 (59)	
Female	33 (42)	75 (41)	71 (37)	78 (41)	
Recipient gender					0.03[b]
Caucasian	57 (72)	116 (63)	138 (72)	139 (72)	
African-American	13 (16)	56 (31)	34 (18)	38 (20)	
Asian/Pacific Islander	3 (4)	4 (2)	12 (6)	12 (6)	
Other/Missing	6 (8)	7 (3)	8 (4)	3 (1)	
Karnofsky performance score prior to transplant					0.002[b]
< 90	30 (38)	96 (52)	77 (40)	101 (53)	
90–100	43 (54)	85 (46)	112 (58)	87 (45)	
Missing	6 (8)	2 (1)	3 (2)	4 (2)	
Sorror HCT-CI					<0.0001[b]
0	20 (25)	22 (12)	46 (24)	26 (14)	
1–2	25 (32)	64 (35)	62 (32)	43 (22)	
3+	34 (43)	95 (52)	81 (42)	119 (62)	
Missing	0	2 (1)	3 (2)	4 (2)	
Disease					<0.0001[b]
AML	39 (49)	115 (63)	94 (49)	111 (58)	
ALL	22 (28)	46 (25)	34 (18)	22 (11)	
CML	4 (5)	10 (5)	12 (6)	3 (2)	
MDS	14 (18)	12 (7)	52 (27)	56 (29)	
Disease Risk Index					
AML	39	115	94	111	0.10[b]
Low	2 (3)	11 (6)	7 (4)	7 (4)	
Intermediate	20 (25)	57 (31)	66 (34)	69 (36)	
High/Very high	15 (19)	44 (24)	18 (9)	29 (15)	
Missing	2 (3)	3 (2)	3 (2)	6 (3)	
ALL	22	46	34	22	0.49[b]
Intermediate	15 (19)	23 (13)	20 (10)	14 (7)	

Variable	MAC-BM	MAC-PB	RIC-BM	RIC-PB	P-Value
High/Very high	7 (9)	23 (13)	14 (7)	8 (4)	
CML	4	10	12	3	0.03[b]
Low	4 (5)	9 (5)	12 (6)	1 (1)	
Intermediate	0	1 (1)	0	1 (1)	
High/Very high	0	0	0	1 (1)	
MDS	14	12	52	56	0.15[b]
Intermediate	7 (9)	4 (2)	27 (14)	14 (7)	
High/Very high	6 (8)	7 (4)	23 (12)	37 (19)	
Missing	1 (1)	1 (1)	2 (1)	5 (3)	
HLA matching					0.19[b]
Haploidentical (1-antigen mismatch)	5 (6)	8 (4)	6 (3)	10 (5)	
Haploidentical (2-antigen mismatches)	74 (94)	173 (95)	181 (94)	182 (95)	
Haploidentical (mismatch number unknown)	0	2 (1)	5 (3)	0	
Donor type					< 0.001[b]
Parent donor	11 (14)	37 (20)	14 (7)	9 (5)	
Offspring donor	30 (38)	58 (32)	120 (63)	124 (65)	
Sibling donor	34 (43)	88 (48)	56 (29)	54 (28)	
Missing	4 (5)	0	2 (1)	5 (3)	
Donor age, years					< 0.001[b]
Median (range)	38 (12–65)	37 (9–68)	37 (8–73)	39 (8–71)	0.44[a]
< 29	25 (32)	52 (28)	55 (29)	43 (22)	
30–49	38 (48)	70 (38)	98 (51)	112 (58)	
50	12 (15)	60 (33)	35 (18)	34 (18)	
Missing	4 (5)	1 (1)	4 (2)	3 (2)	
Time from diagnosis to transplant, months					0.13[b]
Median (range)	6 (3–180)	8 (2–144)	9 (<1–291)	8 (2–171)	0.16[a]
< 6	38 (48)	75 (41)	58 (30)	77 (40)	
6 – <12	18 (23)	47 (26)	64 (33)	52 (27)	
12	23 (29)	61 (33)	70 (36)	63 (33)	
CD34 cell dose, $\times 10^6$/kg					<0.001[b]
Median (range)	3 (0–8)	5 (0–21)	3 (0–13)	6 (0–20)	<0.001[a]
< 2	28 (35)	4 (2)	49 (26)	8 (4)	
2 – <4	31 (39)	24 (13)	91 (47)	20 (10)	
4 – <8	17 (22)	96 (52)	37 (19)	107 (56)	
8	0	33 (18)	4 (2)	44 (23)	
Missing	3 (4)	26 (14)	11 (6)	13 (7)	
CD3 cell dose, $\times 10^6$/kg					<0.001[b]
Median (range)	0 (0–1)	2 (0–11)	0 (0–12)	2 (0–14)	<0.001[a]

Variable	MAC-BM	MAC-PB	RIC-BM	RIC-PB	P-Value
< 2	55 (70)	48 (26)	120 (63)	70 (36)	
2 – <4	0	54 (30)	0	73 (38)	
4 – <8	0	18 (10)	0	12 (6)	
8	0	2 (1)	1 (1)	1 (1)	
Missing	24 (30)	61 (33)	71 (37)	36 (19)	
D-R gender mismatch					0.69[b]
M/M	34 (43)	62 (34)	82 (43)	74 (39)	
M/F	21 (27)	47 (26)	46 (24)	45 (23)	
F/M	12 (15)	46 (25)	39 (20)	40 (21)	
F/F	12 (15)	28 (15)	25 (13)	33 (17)	
D-R CMV status					0.03[b]
–/–	16 (20)	31 (17)	48 (25)	37 (19)	
–/+	27 (34)	41 (22)	66 (34)	62 (32)	
+/–	7 (9)	16 (9)	16 (8)	14 (7)	
+/+	29 (37)	90 (49)	61 (32)	78 (41)	
Missing	0	5 (3)	1 (1)	1 (1)	
Conditioning regimen					N/A
BU+FLU/CY (MAC)	35 (44)	80 (44)	0	0	
TBI±FLU/CY (MAC)	24 (30)	100 (55)	0	0	
TBI±FLU/CY (RIC)	0	0	159 (83)	167 (87)	
FLU+MEL (RIC)	0	0	29 (15)	19 (10)	
Others	20 (25)	3 (2)	4 (2)	6 (3)	
TBI dose, cGy					
Median (range)	1200 (200–1350)	1200 (200–1200)	200 (200–300)	200 (200–400)	<0.001[a]
Year of transplant					< 0.001[b]
2013	6 (8)	11 (6)	52 (27)	13 (7)	
2014	16 (20)	38 (21)	48 (25)	39 (20)	
2015	20 (25)	61 (33)	40 (21)	69 (36)	
2016	37 (47)	73 (40)	52 (27)	71 (37)	
Follow-up of survivors, months, median (range)	13 (4–49)	14 (6–50)	24 (2–53)	21 (6–50)	

Abbreviations: MAC = Myeloablative, BM = Bone Marrow, PB = Peripheral Blood, RIC = Reduced Intensity Conditioning, HCT-CI = Hematopoietic stem cell transplant comorbidity index, AML = Acute myelogenous leukemia, ALL = Acute lymphoblastic leukemia, CML = Chronic myelogenous leukemia, MDS = Myelodysplastic syndromes, N/A = Not applicable, BU = Busulfan, FLU = Fludarabine, CY = Cyclophosphamide, MEL = Melphalan.

The P-Values were obtained by the following statistical hypothesis tests:

[a] Kruskal-Wallis test

[b] Pearson Chi-Square test

Table 2.

Univariate analysis of transplant outcomes by stem cell source and conditioning regimen intensity

Outcomes	MAC-BM (N = 79) N (95% CI)	MAC-PB (N = 183) N (95% CI)	RIC-BM (N = 192) N (95% CI)	RIC-PB (N = 192) N (95% CI)	p-value
Grade 2–4 acute GVHD at 6 months	36 (25–46)%	46 (39–54)%	30 (23–36)%	36 (30–43)%	0.002
Chronic GVHD at 1 years	24 (15–35)%	40 (32–47)%	20 (14–26)%	34 (27–41)%	<0.001
Grade 3–4 acute GVHD	13 (6–21)%	14 (10–20)%	5 (3–9)%	9 (6–14)%	0.06
Relapse at 1 years	28 (18–39)%	26 (20–33)%	37 (30–44)%	36 (29–43)%	0.16
Non-relapse mortality at 1 years	14 (7–23)%	18 (12–24)%	9 (5–13)%	18 (13–24)%	0.01
GVHD-free, relapse-free survival at 1 years	38 (28–49)%	23 (17–30)%	41 (34–49)%	25 (19–32)%	0.002
cGVHD-free, relapse-free survival at 1 years	42 (31–53)%	26 (20–33)%	43 (36–50)%	26 (19–32)%	0.002
Overall survival at 1 years	67 (56–77–)%	64 (57–71)%	70 (63–76)%	58(51–65)%	0.07
Neutrophil recovery at 100 days [*]	92 (85–97)%	95 (91–98)%	94 (90–97)%	93 (89–96)%	0.004
Platelet recovery at 100 days	78 (67–86)%	85 (79–90)%	90 (85–94)%	89 (84–93)%	0.10

[*]. Number of graft failures: MAC-BM (n=1), MAC-PB (n=4), RIC-BM (n=4), RIC-PB (n=6).

Table 3.

Multivariate analysis of transplant outcomes by stem cell source and conditioning regimen intensity

Outcome	Variable	HR (95% CI)	*P*-value
Primary Endpoints			
Acute GVHD grade II-IV			
	MAC–PB vs MAC–BM	1.10 (0.66–1.82)	0.73
	RIC–PB vs RIC–BM	1.24 (0.84–1.82)	0.28
Chronic GVHD			
	MAC–PB vs MAC–BM	1.56 (0.86–2.82)	0.14
	RIC–PB vs RIC–BM	**1.70 (1.11–2.62)**	**0.01**
Secondary Endpoints			
Acute GVHD grade III-IV			
	MAC–PB vs MAC–BM	0.78 (0.38–1.60)	0.49
	RIC–PB vs RIC–BM	1.93 (0.94–3.96)	0.07
Relapse			
	MAC–PB vs MAC–BM	0.95 (0.59–1.52)	0.82
	RIC–PB vs RIC–BM	0.90 (0.65–1.26)	0.55
Non-relapse mortality			
	MAC–PB vs MAC–BM	1.31 (0.62–2.78)	0.48
	RIC–PB vs RIC–BM	**2.06 (1.15–3.68)**	**0.01**
GVHD-free, relapse-free survival			
	MAC–PB vs MAC–BM	1.32 (0.94–1.85)	0.11
	RIC–PB vs RIC–BM	1.31 (1.02–1.69)	0.03
Chronic GVHD-free, relapse-free survival			
	MAC–PB vs MAC–BM	1.36 (0.94–1.98)	0.10
	RIC–PB vs RIC–BM	1.23 (0.94–1.61)	0.12
Overall survival			
	MAC–PB vs MAC–BM	1.02 (0.64–1.62)	0.93
	RIC–PB vs RIC–BM	1.17 (0.86–1.61)	0.32

Table 4.

Chronic GVHD severity by stem cell source and conditioning regimen

Characteristic	MAC-BM	MAC-PB	RIC-BM	RIC-PB	P-value
Number of patients with chronic GVHD	19	70	43	65	
	N (%)	N (%)	N (%)	N (%)	
Chronic GVHD severity					0.44
Mild	13 (68)	33 (47)	26 (60)	44 (68)	
Moderate	5 (26)	25 (36)	12 (28)	13 (20)	
Severe	1 (5)	11 (16)	5 (12)	8 (12)	
Missing		1 (1)			

Table 5.

Multivariate analysis of chronic GVHD by stem cell source and conditioning regimen intensity based on TED level data

Outcome	Variable	HR (95% CI)	*P*-value
Chronic GVHD			
	MAC-PB vs MAC-BM	1.44 (0.96–2.16)	0.08
	RIC-PB vs RIC-BM	**1.75 (1.24–2.47)**	**0.0015**

Table 6.

Causes of death

	MAC-BM (N = 79)	MAC-PB (N = 183)	RIC-BM (N = 192)	RIC-PB (N = 192)
No. of dead patients	**32**	**75**	**84**	**99**
Cause of death - no. (%)				
Primary disease	16 (50)	35 (47)	60 (71)	45 (45)
Graft failure	1 (3)	1 (1)	2 (2)	0
GVHD	1 (3)	7 (9)	4 (5)	3 (3)
Infection	3 (9)	6 (8)	3 (4)	2 (2)
IPn/ARD	6 (19)	12 (16)	8 (10)	16 (16)
Organ failure	2 (6)	6 (8)	3 (4)	17 (17)
Secondary malignancy	1 (3)	8 (11)	3 (4)	14 (14)
Others	2 (6)	0	1 (1)	2 (2)