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Journal

Transplantation and Cellular Therapy, 21(4)

ISSN

2666-6375

Authors

Logan, Aaron C
Wang, Zhiyu
Alimoghaddam, Kamran
et al.

Publication Date

2015-04-01

DOI

10.1016/j.bbmt.2014.12.036

Peer reviewed

HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2015 April ; 21(4): 746–754. doi:10.1016/j.bbmt.2014.12.036.

ABO mismatch is associated with increased non-relapse mortality after allogeneic hematopoietic cell transplantation

Aaron C. Logan[1], **Zhiyu Wang**[2], **Kamran Alimoghaddam**[3], **Ruby M. Wong**[2], **Tze Lai**[2], **Robert S. Negrin**[4], **Carl Grumet**[5], **Brent R. Logan**[6], **Mei-Jie Zhang**[6], **Stephen R. Spellman**[7], **Stephanie J. Lee**[8], and **David B. Miklos**[4] **An analysis on behalf of the Center for International Blood and Marrow Transplantation (CIBMTR)**

[1]Department of Medicine, Division of Hematology and Blood and Marrow Transplantation, University of California, San Francisco, San Francisco, CA

[2]Health Research and Policy, Stanford University School of Medicine, Stanford, CA

[3]Hematology, Oncology, and Stem Cell Transplantation, Tehran University of Medical Sciences, Tehran, Iran

[4]Department of Medicine, Division of Blood and Marrow Transplantation, Stanford University School of Medicine, Stanford, CA

[5]Department of Pathology, Stanford University School of Medicine, Stanford, CA

[6]Medical College of Wisconsin, Milwaukee, WI

[7]Center for International Blood and Marrow Transplant Research, Minneapolis, MN

[8]Fred Hutchinson Cancer Center, Seattle, WA

Abstract

We evaluated ABO associated outcomes in 1,737 patients who underwent allogeneic hematopoietic cell transplant (allo-HCT) at Stanford University between January 1986 and July 2011. Grafts were 61% ABO matched, 18% major mismatched (MM), 17% minor MM, and 4% bidirectional MM. Median follow-up was 6 years. In multivariate analysis, OS was inferior in minor MM HCT (median 2.1 vs 6.3 years; HR 1.56; 95%CI 1.19-2.05; p=0.001) in comparison with ABO matched grafts. ABO minor MM was associated with an increase in early NRM (18% vs 13%; HR 1.48, 95%CI 1.06-2.06; p=0.02). In an independent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of 435 lymphoma patients receiving mobilized peripheral blood grafts, impairment of OS (HR 1.55; 95%CI 1.07 – 2.25; p=0.021) and increased NRM (HR 1.72; 95%CI 1.11 – 2.68; p=0.03) was observed in recipients of ABO minor MM grafts. A second independent analysis of a CIBMTR dataset including 5,179 patients with AML and MDS identified a non-significant trend toward decreased OS in recipients of ABO minor MM grafts and also found ABO major MM to be significantly associated with decreased

Corresponding author mailing address: David B. Miklos, MD, PhD, Division of Blood and Marrow Transplantation, Stanford University School of Medicine, 269 West Campus Drive CCSR 2205, Stanford, CA 94305; Phone: 650-725-4626; dmiklos@stanford.edu.

Financial Disclosure Statement: The authors have no relevant disclosures.

OS (HR 1.19, 95% CI 1.08 – 1.31, p<0.001) and increased NRM (HR 1.23, 95%CI 1.08 – 1.4, p=0.002). ABO minor and major MM are risk factors for worse transplant outcomes, although the associated hazards may not be uniform across different transplant populations. Further study is warranted to determine which patient populations are at greatest risk, and whether this risk can be modified by anti-B-cell therapy or other peri-transplant treatments.

Keywords

ABO mismatch; allogeneic; transplantation; non-relapse mortality

Introduction

In the setting of allogeneic hematopoietic cell transplantation (allo-HCT) using bone marrow, peripheral blood, or umbilical cord blood, adequate matching between human leukocyte antigens (HLA) is considered to be the only absolute requirement upon which to base donor selections. Other factors such as donor age, gender, parity, ABO type, and CMV serostatus play a secondary role when selecting between multiple HLA-compatible donors.[1, 2] The risk of ABO incompatibility between donors and recipients, though of critical importance during solid organ transplantation, has largely been considered negligible in allo-HCT. This likely derives from a controversial body of literature regarding the contribution of different types of ABO mismatch (MM) to clinical outcomes in allo-HCT patients (reviewed extensively by Rowley *et al.*[3]).

Due to microbial molecular mimicry with ABO antigens, humans are almost uniformly immunized to whichever A or B antigen(s) they do not genetically possess. This phenomenon results in hemolytic transfusion reactions when patients with pre-existing immunity and antibody titers receive incompatible blood products. This scenario is equivalent to ABO major MM in allo-HCT, a setting in which persistence of recipient type anti-ABO antibodies may lead to severe hemolysis of donor red cells, and in some cases, delayed erythrocyte engraftment, red cell aplasia, or even graft failure.[3-11] ABO minor MM, on the other hand, represents a scenario unique to allo-HCT and solid organ transplantation and occurs when donors possess anti-recipient ABO B lymphocytes and antibodies. Because adoptive transfer of such passenger B lymphocytes into a host with abundant cognate antigen may lead to their further stimulation, this scenario has been associated with hemolysis of recipient-derived erythroid elements in the peri-transplant period and has been linked to decreased OS.[12-15] ABO antigens are also widely expressed on vascular and lymphatic endothelium, peri-vascular connective tissues, and bile duct epithelium, so tissue targeting by adoptively transferred B cells may extend beyond hematopoietic tissues.[16, 17]

We retrospectively evaluated the patient characteristics and clinical outcomes of 1737 patients who underwent allo-HCT at Stanford University Medical Center between January 1986 – July 2011. We observed that ABO minor MM was associated with a significant decrement in overall survival (OS) and an increase in non-relapse mortality (NRM). To corroborate our findings, we requested the Center for International Bone and Marrow

Transplant Research (CIBMTR) re-evaluate data that contributed to two existing publications that did not previously evaluate the role of donor-recipient ABO matching.

Patients and Methods

Patients—single institution

A total of 1737 patients who underwent allo-HCT at Stanford University or Lucille Packard Children's Hospital between January 1986 and July 1, 2011, and who provided informed consent for retrospective access to their records were included in our analysis. Access to all records was in compliance with, and supervised by, the Stanford University School of Medicine Institutional Review Board. Diagnoses amongst this single-institution cohort included acute myeloid and lymphoblastic leukemia (AML/ALL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), primary myelofibrosis, unspecified myeloproliferative disorders, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), mycosis fungoides, multiple myeloma, severe aplastic anemia, hemophagocytic lymphohistiocytosis and other inherited and acquired cytopenias, sickle cell anemia and other inherited hemoglobinopathies, Hurler syndrome and other inherited metabolic syndromes, Wiskott-Aldrich syndrome and other primary immune deficiency syndrome, osteopetrosis, renal cell carcinoma, and systemic lupus erythematosus. Patient ages ranged from birth to 74 years old.

Myeloablative (MA) conditioning regimens were comprised of those based on high-dose chemotherapy (carmustine, cyclophosphamide, and etoposide; busulfan and cyclophosphamide; busulfan, etoposide, and cyclophosphamide; high-dose cyclophosphamide; melphalan, thiotepa, and fludrabine) or based on high-dose radiation with chemotherapy (fractionated total body irradiation [FTBI] with cyclophosphamide; FTBI with etoposide; FTBI with etoposide and cyclophosphamide; FTBI, cytarabine, and cyclophosphamide) with or without incorporation of immunosuppressive antibody therapy (e.g., anti-thymocyte globulin [ATG] or alemtuzumab). Non-myeloablative (NMA) regimens included those with non-ablative dose chemotherapy alone (fludarabine and cyclophosphamide; fludarabine, carmustine, and melphalan) and those combining radiation with cytotoxic immunosuppression or chemotherapy (FTBI with fludarabine; total lymphoid irradiation [TLI] with ATG; electron beam therapy with TLI and ATG) with or without additional immunosuppressive antibody treatments. Grafts were derived from bone marrow or G-CSF mobilized peripheral blood stem cells (PBSC) apheresis products. Patients receiving cord blood, haploidentical, or syngeneic grafts were excluded from analysis.

Immunosuppressive regimens largely consisted of a calcineurin inhibitor (either cyclosporine or tacrolimus) combined with either methotrexate or other agents, including corticosteroids, mycophenolate mofetil, or sirolimus. Immunosuppressive regimens were selected either as standard of care, or in some cases, were exploratory combinations evaluated in the setting of clinical trials.

Donors and recipients underwent HLA typing by serology until 1998, since when high-resolution molecular typing for HLA-A, -B, -C, -DRB1, and -DRQ1 was performed. All donors and recipients were serologically tested for presence of anti-CMV IgG to determine

prior viral exposure, and attempts were made to pair CMV negative recipients with CMV negative donors. ABO typing was performed by routine to ensure safe blood transfusion support during the peri-transplant period. No specific conditioning or immunosuppressive regimens were selected for any patient on the basis of ABO incompatibility.

Patients — Multiple institution (CIBMTR—Ratanatharathorn *et al.*[18])

As a corroborating analysis, we re-analyzed an existing data set created by the CIBMTR to study the effect of pre-transplant Rituximab on survival and graft-versus-host disease.[18] This cohort consisted of 435 B-cell non-Hodgkin lymphoma patients who underwent T-cell replete allo-HCT with G-CSF mobilized peripheral blood from 1999 to 2004. Patients who had received anti-CD52, anti-T cell antibodies, or T-cell depleted grafts were excluded. A total of 179 of these patients received Rituximab during the 6 months prior to HCT, while 256 patients did not. The existing multivariate analyses which contributed to the Ratanatharathorn *et al.*[18], publication were updated to include ABO match, major MM, minor MM and bidirectional MM to test the hypothesis that ABO matching was independently associated with transplant outcomes.

Patients — Multiple institution (CIBMTR—Luger *et al.*[19])

We also re-analyzed an existing CIBMTR dataset addressing outcomes in patients undergoing allo-HCT for AML and MDS.[19] The Luger *et al*.[19] study focused on the relative efficacy of MA (3731 patients) and NMA (1448 patients) conditioning regimens. Definitions of regimen intensity follow established guidelines,[20] and can be found in the original publication.[19] All patients received T cell replete grafts from mobilized peripheral blood or bone marrow. ABO match, major MM, minor MM, and bidirectional MM were added as variables to test the hypothesis that ABO matching was independently associated with transplant outcomes.

Definition of Outcomes

Our primary outcomes of interest were OS and NRM. OS was defined as the number of days between graft infusion (day 0) and death from any cause. NRM was defined as death from any cause other than recurrence of the disease for which the patient underwent allo-HCT. Event-free survival was defined as the number of days between graft infusion and either relapse or death from any cause. Acute graft-versus-host disease (GVHD) grades 2 though 4 were graded clinically according to the Glucksberg scale.[21] Clinical relapse was determined according to accepted clinical criteria for each disease type.

Statistical Methods

Medians and ranges are reported for patient ages and time to events. Percentages are reported for categorical variables. Probabilities of overall survival (OS) and event-free-survival (EFS) were estimated using the Kaplan-Meier method.[22] For OS, death from any cause was defined as an event, with surviving patients censored at last follow-up time from BMT date. For EFS analyses, either relapse or death was defined as an event, censoring surviving patients without relapse. The log-rank test was used to compare survival curves.

All univariate and multivariate analyses were performed using proportional hazards models to calculate relative risks and their 95% confidence intervals.[23]

Cumulative incidence functions with competing risks[24] were used to estimate the probabilities of relapse, non-relapse mortality, non-relapse mortality up to day 100, and acute GVHD grades 2-4 or 3-4. Probabilities of relapse were estimated with relapse as an event and NRM as a competing risk. For NRM and NRM at day 100 estimations, non-relapse death was an event, with relapse being the competing risk. For NRM at day 100, the time horizon is 100 days post BMT — events up to day 100 are included, with all other observations with at least 100 days of follow-up time censored at day 100.

For probabilities of acute GVHD grades 2-4 and 3-4, death was the competing risk in the model. Since the longest time to acute GVHD was 125 days in the Stanford patient cohort, non-event observations with at least 125 days of follow-up were censored at day 125. Cumulative incidence curves were compared according to Fine and Gray.[25]

Two multivariate analysis models were used to accommodate interactions between graft type (bone marrow or peripheral blood) and ABO minor mismatch observed in the Stanford cohort. In one analysis, a mixture model was created to determine whether, for either graft type, any of the ABO mismatch categories was associated with survival. In this model, the interaction between graft type and ABO mismatch was represented by using interaction terms as covariates in the Cox regression model for overall survival.[26, 27] In the second model, eight composite variables were created to indicate all combinations of graft source (bone marrow or peripheral blood) and ABO matching status and interactions were tested for each ABO match status by pairwise comparison of hazard ratios.

Results

Patient characteristics—single institution study (Stanford)

Characteristics of the 1737 patients undergoing allo-HCT at Stanford University Medical Center between January 1986 and July 2011 are shown in Table 1. In this single institution cohort, 1053 (60.6%) patient/donor pairs were ABO matched, 297 (17.1%) were ABO minor mismatched, 309 (17.8%) were ABO major mismatched, and 78 (4.5%) were ABO bidirectionally mismatched. Patient characteristics within each ABO compatibility group are shown in Supplemental Table 1. Patients generally fit into two large categories by diagnosis: 1) Leukemia group (acute myeloid and lymphoid leukemias, MDS, and CML), and 2) Lymphoma group (non-Hodgkin lymphomas and chronic lymphocytic leukemia), with a relatively small number of patients with other diagnoses. Roughly 75% of patients received related donor grafts, whereas the remaining 25% received grafts from unrelated adult donors. A total of 1211 (70%) underwent myeloablative conditioning, while 526 (30%) received reduced intensity conditioning. For statistical analyses, we divided treatment eras into: 1) 1986-1997, and 2) 1998-2004 group (prior to advent of bone marrow graft plasma depletion) and 3) 2005-July 1, 2011 (all grafts were plasma depleted).

Clinical outcomes with ABO minor mismatched allo-HCT

ABO minor MM between donor and recipient was uniquely associated with a range of clinical events, including premature death (Table 2). ABO major and bidirectional MM were not significantly associated with any survival endpoints. Across the entire group studied, the presence of ABO minor MM between donor and recipient was associated with significantly decreased overall survival (p=0.005) (Figure 1A). To further elucidate the characteristics of the patients and the clinical outcomes associated with this finding, we assessed the impact of ABO minor MM on NRM and acute GVHD. Patients receiving ABO minor mismatched grafts had a significantly higher risk of NRM (overall univariate HR 1.34, 95%CI 1.06 – 1.69; p=0.015) (Figure 1B and Table 2). Interestingly, this significant disparity in NRM was already apparent before day 100 (HR 1.41, 95%CI 1.03 – 1.94, p=0.033), but acute GVHD grade 2-4 was not significantly different between the two groups (HR 1.6, 95%CI 0.96 – 1.64, p=0.094). As a result of increased NRM, median overall survival was just 2.1 years in the ABO minor mismatch recipients, while it was 6.3 years in the ABO matched recipients (Table 2).

Graft source effect on ABO minor mismatched allo-HCT

Although the majority of allografts for malignant conditions at Stanford have been derived from G-CSF mobilized PBSC since roughly 2000, the outcomes of a substantial number of bone marrow graft recipients, including 455 ABO matched and 119 ABO minor mismatched sources, were included in this retrospective analysis (Supplemental Table 2). Bone marrow grafts were highly associated with the ABO minor mismatch effect, with significantly decreased OS (HR 1.7, 95%CI 1.3 – 2.2, p=0.0002) and EFS (HR 1.6, 95%CI 1.2 – 2.1; p=0.0005), and increased NRM (HR 1.8, 95%CI 1.3 – 2.5, p=0.0004). Amongst the bone marrow graft recipients, we also observed that the NRM at day 100 was significantly higher in recipients of ABO minor mismatched grafts (HR 2.0, 95%CI 1.3 – 3.0, p=0.001), and that there was an associated increase in acute GVHD grades 2-4 (HR 1.6, 95%CI 1.1 – 2.4, p=0.025) and grades 3-4 (HR 2.4, 95%CI 1.4 – 4.1, p=0.001). Peripheral blood grafts did not demonstrate a significant difference in the outcomes of ABO matched and minor mismatched grafts (Supplemental Table 2), and no other ABO incompatibilities were associated with significant outcome effects.

Multivariate analyses of single and multi-institution cohorts

The predominance of the ABO minor MM effect in bone marrow grafts but not in peripheral blood grafts as shown in Supplemental Table 2 implies a differential effect based on graft type. This interaction was accommodated in two multivariate approaches that included all patients. First, a mixture model evaluating outcomes with bone marrow and peripheral blood grafts based on whether ABO minor MM was present and accounting for other covariates listed in the legend of Table 3 was employed. In this interaction model, ABO minor MM remained a risk for decreased OS (HR 1.56, 95%CI 1.19 – 2.05; p=0.001) and increased NRM (HR 1.48, 95% CI 1.06 – 2.06; p=0.02) (Table 3). In the second model, pairwise comparisons of hazard ratios with eight composite variable accounting for all combinations of graft source and ABO matching status showed that ABO minor MM with bone marrow was associated with lower OS (p=0.001) and higher NRM (p=0.02) than ABO matched bone

marrow. Among peripheral blood recipients, all ABO MM combinations had hazard ratios that were not significantly different than the ABO matched group (OS, p>0.8, and NRM, p>0.4).

To better assess the risk of ABO mismatch in lymphoma patients, we analyzed an existing lymphoma patient dataset previously compiled by Ratanatharathorn *et al*. and the CIBMTR for ABO effects.[18] Patients in this data set were all diagnosed with B-cell NHL and underwent T-cell replete peripheral blood stem cell transplantation. When the original study was performed, ABO compatibility was not included in the multivariate models. We thus re-evaluated this relatively homogeneous patient population for the impact of ABO mismatch on clinical outcomes. ABO status of both donor and recipient was known for 408 patients, with 240 (59%) ABO matched, 73 (18%) minor mismatched, 73 (18%) major mismatched, and 22 (5%) bidirectionally mismatched.

In Cox regression analysis, ABO minor MM was associated with impaired OS in comparison with ABO matched pairs (HR 1.55, 95%CI 1.07 – 2.25; p=0.021) (Figure 2A and Table 3). ABO minor mismatch also was significantly associated with increased NRM (HR 1.72, 95%CI 1.11 – 2.68; p=0.016), (Figure 2C and Table 3). ABO mismatch did not significantly associate with relapse, acute GVHD grades 2-4 or 3-4, or chronic GVHD (data not shown).

To address ABO mismatch effects in patients with myeloid diseases treated at multiple institutions, we also re-evaluated an existing CIBMTR dataset addressing the outcome of 5,179 patients allografted with MA or NMA preparations for AML and MDS.[19] All types of ABO MM exhibited a trend toward decreased OS in comparison with ABO matched grafts (Figure 2B), but only ABO major MM was found to be significantly associated with decreased OS (HR 1.19; 95%CI 1.08 – 1.31; p<0.001) and increased NRM (HR 1.23; 95%CI 1.08 – 1.40; p=0.002) (Figures 2B and 2D). ABO minor MM was not significantly associated with changes in OS (HR 1.06, 95%CI 0.97 – 1.16, p=0.24) or NRM (HR 1.07, 95%CI 0.94 – 1.21; p=0.33).

Discussion

This study describes the effect of ABO mismatch on outcomes in patients undergoing related and unrelated donor allo-HCT for all indications at a single institution (Stanford University), and in two published CIBMTR registry studies which did not previously account for ABO mismatch in multivariate models of hazards for NRM and OS.[18, 19] In the Stanford cohort of 1737 patients transplanted between 1986 and 2011, we identified a significant impairment in OS (univariate HR 1.27, 95%CI 1.07 – 1.52, p=0.005; multivariate HR 1.56, 95%CI 1.19 – 2.05, p=0.001) in patients receiving ABO minor MM grafts, while other forms of ABO mismatch were not significantly associated with outcome (Figure 1A, Table 2 and Table 3). The survival decrement in recipients of ABO minor MM grafts is attributable to increased NRM (univariate HR 1.34, 95%CI 1.06 – 1.69, p=0.015; multivariate HR 1.48, 95%CI 1.06 – 2.06, p=0.02), with risk of mortality being evident prior to day 100 post-transplant. A non-significant trend toward increased aGVHD grades 2-4 was

noted, but the pathophysiology of ABO minor MM-related events remains to be better elucidated.

In the Stanford analysis, we noted an interaction between ABO minor MM and bone marrow grafts, which is consistent with bone marrow having a higher relative fraction of B lymphocytes to be adoptively transferred into recipients.[28] In recipients of ABO minor MM bone marrow grafts, an increased risk of aGVHD was observed (HR 1.6, 95%CI 1.1 – 2.4, p=0.025; Supplemental Table 2). No form of ABO incompatibility was associated with NRM or survival outcomes in recipients of PBSC grafts at Stanford. Interestingly, however, the CIBMTR (Ratanatharathorn *et al.*[18]) analysis revealed increased risk of NRM (multivariate HR 1.72, 95%CI 1.11 – 2.68, p=0.02) and decreased OS (multivariate HR 1.55, 95%CI 1.07 – 2.25, p=0.021) with ABO minor MM grafts in a relatively homogeneous cohort of lymphoma patients, all of whom received PBSC grafts (Figures 2A and 2C), suggesting the attributable risks of this form of ABO incompatibility may not exclusively be present with marrow grafts. It is likely host features interact with adoptively transferred lymphocytes from ABO mismatched donors in ways that are not evident from this study. It is also possible that the differences in risk with ABO minor MM PBSC grafts between Stanford and the multi-institution Ratanatharathorn *et al.*[18] study could potentially be related to differences in the composition or handling of PBSC grafts, administered cell dose at different institutions, or management of post-transplant immune suppression tapers. It is also possible that lymphoma patients, being lymphopenic from lymphotoxic therapies for their primary disease, may experience increased post-transplant homeostatic expansion of adoptively transferred donor B cells leading to enhanced activation of relevant anti-ABO lymphocytes. This phenomenon might be expected in patients who do not have residual bioactive Rituximab *in vivo* at the time of adoptive lymphocyte transfer, and reduced in patients treated with Rituximab within 6 months prior to adoptive lymphocyte transfer.

While we identified NRM and OS risks with ABO minor MM in both the Stanford and CIBMTR (Ratanatharathorn *et al.*[18]) analyses, the same effect was not observed in the CIBMTR (Luger *et al.*[19]) analysis of 5179 patients transplanted at 223 centers in 37 different countries.[19] The Luger *et al.*[19] study included exclusively patients with AML and MDS, but a mixture of BM and PBSC grafts (2333 vs 2846) and myeloablative and RIC/NMA conditioning (3731 vs 1448). The reasons for the difference in the impact of ABO minor MM grafts in this study in comparison with the other studies remains unclear, but it is possible that the relatively low OS in this cohort (34% for myeloablated recipients, 33% for RIC, and 26% for NMA conditioning) impacted the ability to detect OS differences in ABO subsets. It is also possible that management of other ABO incompatibilities differed across this multi-institution cohort in comparison with Stanford and the Ratanatharathorn et al.[18] study sites, leading to lower relative importance of ABO minor MM. Instead, ABO major mismatches were associated with worse survival and higher NRM (Figures 2B and 2D).

Watz and colleagues recently reported an analysis of transplant outcomes in 310 patients undergoing reduced intensity conditioning and identified increased risk of NRM in patients receiving ABO minor MM allografts and meeting criteria for passenger lymphocyte syndrome (PLS), defined as detection of donor type anti-ABO antibodies within one month

of transplant.[29] In their study, six patients out of 66 with ABO minor MM grafts met these criteria and their survival was 0% versus 61% in patients without PLS ($p<0.001$); however, deaths were more frequently associated with relapse than NRM, and the generalizability of these data are unclear since most of the patients experiencing PLS underwent allo-HCT for solid tumors. None of the patients in the cohorts we studied had available data regarding anti-ABO antibody titers post-transplant, so we are unable to explore the effect of such antibodies or their utility as biomarkers of PLS. Nevertheless, measurement of donor type anti-ABO antibodies during the early post-HCT period could prove useful for better understanding the incidence of PLS and whether objective markers of adoptively transferred lymphocyte activation can predict negative immunologic sequelae of ABO minor MM grafts.

If donor type anti-ABO antibodies are pathogenic or strongly correlate with PLS, a useful therapeutic maneuver would be the administration Rituximab or other anti-B cell therapy peri-transplant to ablate adoptively transferred B lymphocytes. We attempted to evaluate the Stanford dataset for possible beneficial effect from the administration of Rituximab within 6 months prior to allo-HCT; however, the number of patients for whom this data was available was limited. There was, nevertheless, a suggestion of possible benefit in 33 ABO minor mismatch patients with NHL and CLL patients who received Rituximab within 6 months prior to allo-HCT, with improved OS (HR 0.4, 95%CI 0.2 – 0.9, p=0.02) and decreased NRM (HR 0.3, 95%CI 0.1 – 0.9, p=0.03) in comparison with 19 NHL/CLL ABO minor mismatch patients who did not receive peri-HCT Rituximab. Similarly, the CIBMTR (Ratanatharathorn *et al.*[18]) study demonstrated decreased OS in 44 recipients of ABO minor mismatched PBSC grafts longer than 6 months after the last dose of Rituximab (HR 1.6 vs ABO matched grafts, 95%CI 1.03 – 2.5, p=0.037), whereas the survival of 29 patients receiving ABO minor mismatched grafts within 6 months of last Rituximab dose was not significantly different from that of patients receiving ABO matched grafts (HR 1.44, 95%CI 0.75 – 2.79, p=0.27). A complete analysis of these outcomes in the Stanford and CIBMTR (Ratanatharathorn *et al.*[18]) datasets is not provided in this manuscript, because we are hesitant to make conclusions from these small numbers of patients. We believe these preliminary findings can only be considered hypothesis generating with respect to a possible method for ameliorating the risk of ABO minor MM in allo-HCT that deserves further study in a multi-institution prospective study.

In our study, ABO major MM was shown to be a significant hazard for increased NRM and decreased OS in the AML/MDS CIBMTR (Luger *et al.*[19]) analysis, but not in the lymphoma CIBMTR (Ratanatharathorn *et al.*[18]) study or the single institution Stanford study. It is possible the management of ABO major MM associated hemolytic and red cell aplasia events differed across the various study sites, leading to the difference in hazard ratios. Hemolysis and red cell aplasia resulting from recipient type anti-donor ABO antibodies may be managed with supportive red blood cell transfusion (conveying the risk of transfusional iron overload), erythrocyte stimulating agents (conveying the risk of thrombosis), intravenous immune globulin, or manipulations of immunosuppression that cannot be assessed from registry data. The risk of hemolytic events may also be modified by the quality of erythrocyte cross-matching and avoidance of other red cell antigen-antibody

incompatibilities. ABO major MM may also be associated with delayed platelet engraftment, which may convey risks in the post-HCT setting and increase NRM risk in some populations.[30]

Watz and colleagues also presented a possible explanation for deleterious effects in patients receiving ABO major MM allografts.[29] Ninety-five of the 310 patients they studied received ABO major MM grafts, and 12 of those patients developed persistent or recurring recipient type anti-ABO antibodies (PRABO). Patients with PRABO had significantly increased NRM (50% versus 21%, p=0.03) and decreased 3-year OS (17% versus 73%, p=0.002).[29] Interestingly, patients with PRABO had an increased incidence of hemolytic anemia, which is to be expected, but a decreased incidence of acute and chronic GVHD. Management of PRABO-associated hemolysis was not detailed and the reasons for decreased GVHD but higher NRM with lower OS remain uncertain, but could be associated with the therapies used to treat sequelae of ABO major MM, additional blood product support and iron overload toxicity, or the finding may be spurious given the small sample size. Again, though, routine post-transplant measurement of anti-ABO antibodies and capture of such data in transplant databases could prove useful for better understanding the incidence of hemolysis and other associated negative outcomes in ABO major MM.

To our knowledge, the data we have presented here represent one of the largest analyses of ABO incompatibility in allo-HCT. Nevertheless, several other retrospective studies have identified ABO minor and major MM as risks in the setting of allo-HCT,[31] and ours is not the first study to find contradictory results when assessing the impact of ABO incompatibilities in different patient populations.[3] As with other studies, a consistent and universal pattern for risks associated with ABO incompatibility fails to emerge from our study. Nevertheless, we identified risk for increased NRM and decreased OS with ABO minor MM in two of the three cohorts we studied, which adds to other studies that have identified minor MM as a survival risk. ABO minor MM HCT provides an attractive model for additional study of adoptive lymphocyte transfer since activation of donor lymphocytes can be measured by the titer of donor type anti-ABO antibodies, and methods for reducing the production of such antibodies exist, as discussed above. We conclude that systematic measurement of anti-ABO antibodies after allo-HCT and capture of such data in transplant registries should be pursued to enhance understanding of the kinetics of donor lymphocyte activation and the clinical events associated with anti-ABO antibodies in ABO incompatible allo-HCT. Lastly, we conclude from this study that an ABO matched donor is preferable to an ABO mismatched donor, when the option exists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the nursing staff, social workers, case managers, physical therapists, dieticians, and data managers who made the care of the patients described herein possible. The care of these patients, and the management of data were supported by NIH P01CA049605. We also wish to acknowledge the critical contribution of Dr. Karl Blume (1937 – 2013) who established robust data collection at the beginning of the Stanford Blood and Marrow Transplant program, thus enabling this research. The CIBMTR is supported by Public Health Service Grant/

Cooperative Agreement U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-13-1-0039 and N00014-14-1-0028 from the Office of Naval Research; and grants from Actinium Pharmaceuticals; Allos Therapeutics, Inc.; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; Blue Cross and Blue Shield Association; Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech North America, Inc.; Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; Remedy Informatics; Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; TerumoBCT; Teva Neuroscience, Inc.; THERAKOS, Inc.; University of Minnesota; University of Utah; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

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Highlights

- ABO minor and major mismatches between donors and recipients of hematopoietic allografts are associated with increased non-relapse mortality and decreased overall survival.
- The associated hazards of ABO minor and major mismatches are not uniform across different transplant populations.
- An ABO matched donor is preferable to an ABO mismatched donor, when the option exists.

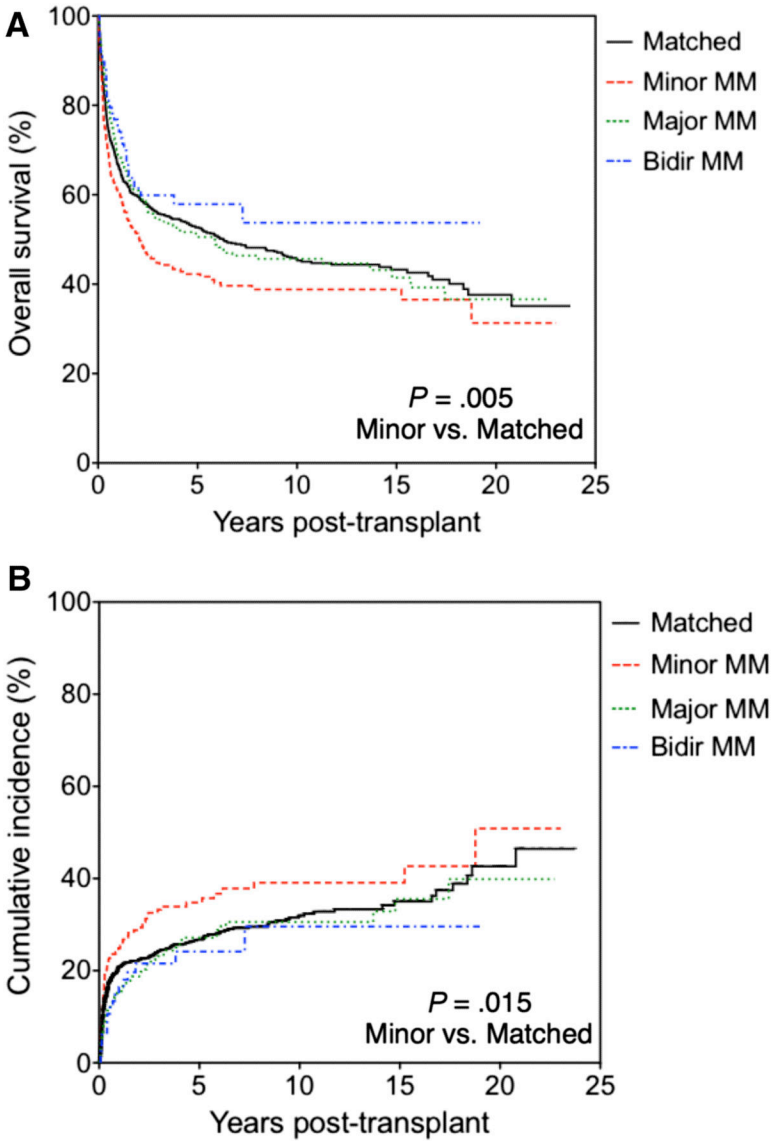

Figure 1.

Recipient survival when donor was ABO matched, minor mismatched, major mismatched, or bidirectionally mismatched. Recipients receiving minor mismatched grafts experienced a significant overall survival impairment compared with those receiving ABO matched grafts (p=0.005) (A). Cumulative incidence of non-relapse mortality was increased in recipients of ABO minor mismatched grafts compared with recipients of ABO matched grafts (p=0.015) (B).

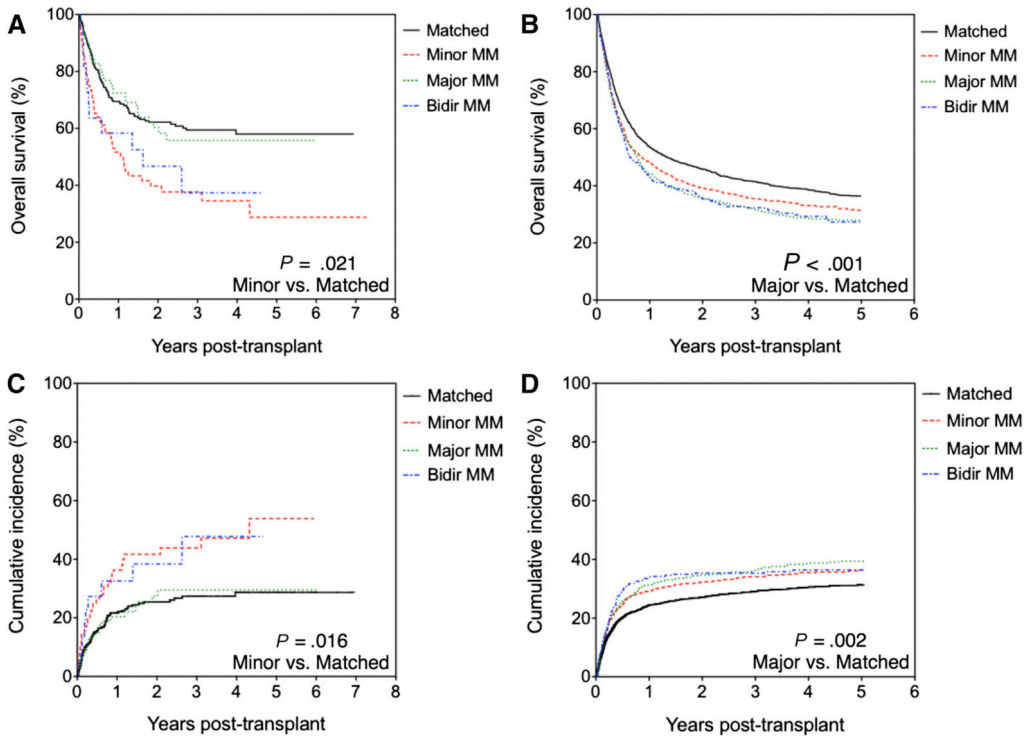

Figure 2.

Center for International Blood and Marrow Transplantation analysis of overall survival and cumulative incidence of non-relapse mortality in patients receiving ABO matched, minor MM, major MM, or bidirectionally (Bidir) MM hematopoietic allografts for lymphoma (A and C; data from Ratanatharathorn et al.[18] evaluated for ABO effect) or AML/MDS (B and D; data from Luger et al.[19] evaluated for ABO effect). MM = mismatch

Table I

Patient characteristics

Variable	Stanford	CIBMTR (Ratanatharathorn)	CIBMTR (Luger)
No. patients	1737	435	5179
Median age, y (range)	41 (0-73)	50 (22-70)	45 (18-70)
Age group			
<21	392 (22)	0	208 (4)
21-39	472 (27)	77 (18)	1677 (32)
40-59	704 (41)	316 (73)	2791 (54)
>=60	168 (10)	42 (10)	503 (10)
Recipient gender, male			
female	733 (42)	145 (33)	2331 (45)
male	1004 (58)	290 (67)	2848 (55)
Diagnosis			
AML/MDS/CML	1184 (68)	0	5179 (100)
NHL/CLL	302 (17)	435 (100)	0
Other	251 (15)	0	0
Donor			
Related	1303 (75)	330 (76)	2079 (40)
Unrelated	434 (25)	105 (24)	3100 (60)
Graft type			
PB	997 (57)	435 (100)	2846 (55)
BM	727 (42)	0	2333 (45)
Unknown	13 (1)	0	0
Regimen			
Ablative	1211 (70)	197 (45)	3731 (72)
Reduced-intensity	526 (30)	238 (55)	1448 (28)
ABO			
Matched	1053 (61)	240 (59)	2608 (50)
Minor mismatch	297 (17)	73 (18)	1084 (21)
Major mismatch	309 (18)	73 (18)	977 (19)
Bidirectional mismatch	78 (4)	22 (5)	311 (6)
Unknown	0	0	199 (4)
Donor / Recipient gender			
M / M	550 (32)	167 (38)	1832 (35)
M / F	431 (25)	78 (18)	1296 (25)
F / M	454 (26)	123 (28)	1016 (20)
F / F	302 (17)	64 (15)	1035 (20)
Donor / Recipient CMV status			
D neg / R neg	403 (23)	123 (28)	1317 (25)
D neg / R pos	338 (20)	94 (22)	1375 (27)
D pos / R neg	204 (12)	62 (14)	576 (11)

Variable	Stanford	CIBMTR (Ratanatharathorn)	CIBMTR (Luger)
D pos / R pos	562 (32)	134 (31)	1735 (34)
Unknown	230 (13)	22 (5)	176 (3)
Primary immunosuppression			
CSA +/- other	651 (37)	129 (30)	833 (16)
CSA + MTX +/- other	372 (21)	149 (34)	2804 (54)
FK +/- other	87 (5)	47 (11)	423 (8)
FK + MTX +/- other	175 (10)	103 (24)	1119 (22)
Other	136 (8)	7 (2)	0
Unknown	316 (18)	0	0
Transplant era			
1987 - 1997	446 (26)	0	~
1998 - 2004	499 (29)	435 (100)	5179 (100)
2005 - July 1, 2011	792 (46)	0	0
Median f/u, survivors, y (range)	6.0 (0.3 - 23.7)	4.3 (0.25 - 7.3)	1 (0.09 - 10.7)

Table 2

Patient outcomes with ABO matched or ABO mismatched grafts (all diagnoses).

Event	ABO Matched	ABO Minor MM	ABO Major MM	ABO Bidir MM
Total patients	1053	297	305	78
Overall survival, y, median	6.3	2.1	5.87	NR
Number of events	526	167	153	32
HR (c.i.)	1	**1.27 (1.07 - 1.52)**	0.98 (0.82 - 1.18)	0.8 (0.56 - 1.5)
P-value	–	**0.005**	0.87	0.22
EFS, y, median	2.7	1.2	2.08	7.27
Number of events	606	183	180	37
HR (c.i.)	1	**1.2 (1.02 - 1.42)**	1.02 (0.86 - 1.21)	0.8 (0.57 - 1.11)
P-value	–	**0.028**	0.81	0.18
Relapse				
Number of events	328	89	107	20
HR (c.i.)	1	1.09 (0.86 - 1.37)	1.12 (0.9 - 1.4)	0.78 (0.5 - 1.23)
P-value	–	0.49	0.3	0.29
NRM, overall				
Number of events	278	94	73	17
HR (c.i.)	1	**1.34 (1.06 - 1.69)**	0.89 (0.69 - 1.15)	0.82 (0.5 - 1.34)
P-value	–	**0.015**	0.38	0.42
NRM, day 100				
Events @ d100	137	53	25	5
HR (c.i.)	1	**1.41 (1.03 - 1.94)**	**0.62 (0.4 - 0.95)**	0.48 (0.2 - 1.18)
P-value	–	**0.033**	**0.027**	0.11
aGVHD, gr2-4				
Events @ d125	220	72	61	14
HR (c.i.)	1	1.26 (0.96 - 1.64)	0.95 (0.72 - 1.26)	0.87 (0.51 - 1.49)
P-value	–	0.094	0.73	0.6
aGVHD, gr3-4				
Events @ d125	166	35	29	10
HR (c.i.)	1	1.14 (0.78 - 1.67)	0.77 (0.51 - 1.17)	1.22 (0.64 - 2.3)
P-value	–	0.49	0.23	0.55

Table 3

Multivariate Cox regression analysis of ABO mismatch effect on overall survival and non-relapse mortality. Significant associations are shown in bold text.

Event	ABO Matched	ABO Minor MM	ABO Major MM	ABO Bidir MM
Overall survival, Stanford*				
Number evaluable	1049	293	309	78
HR (c.i.)	1	**1.56 (1.19 - 2.05)**	1.02 (0.85 - 1.23)	0.87 (0.61 - 1.26)
P-value	–	**0.001**	0.82	0.82
Overall survival, CIBMTR (Ratanatharathorn)*				
Number evaluable	240	73	73	22
HR (c.i.)	1	**1.55 (1.07 - 2.25)**	0.86 (0.57 - 1.31)	0.94 (0.37 -2.39)
P-value	–	**0.021**	0.49	0.91
Overall survival, CIBMTR (Luger)**				
Number evaluable	2540	1065	955	308
HR (c.i.)	1	1.06 (0.97 - 1.16)	**1.19 (1.08 - 1.31)**	1.13 (0.97 - 1.31)
P-value	–	0.24	**<0.001**	0.11
NRM, Stanford*				
Number evaluable	1049	293	309	78
HR (c.i.)	1	**1.48 (1.06 - 2.06)**	0.91 (0.7 - 1.18)	0.94 (0.57 - 1.55)
P-value	–	**0.02**	0.47	0.81
NRM, CIBMTR (Ratanatharathorn)*				
Number evaluable	240	73	73	22
HR (c.i.)	1	**1.72 (1.11 - 2.68)**	0.87 (0.52 - 1.46)	1.42 (0.69 - 2.9)
P-value	–	**0.02**	0.6	0.34
NRM, CIBMTR (Luger)**				
Number evaluable	2540	1065	955	308
HR (c.i.)	1	1.07 (0.94 - 1.21)	**1.23 (1.08 - 1.4)**	1.11 (0.9 - 1.36)
P-value	–	0.33	**0.002**	0.35

* Variables included in the model are: ABO match (matched vs. minor mismatched vs. major mismatched vs. bidirectional mismatched), diagnosis category (leukemia vs. lymphoma vs. other), age at transplantation (<=20, 21-39,40-59, >=60), recipient gender (male vs. female), donor relatedness (HLA-identical sibling vs. unrelated), graft type (PBSC vs. bone marrow), indicator of joint ABO minor MM and PBSC, regimen type (myeloablative vs. non-myeloablative), transplant era (before 1998 vs. 1998 - 2004 vs. after 2004). The significant covariates for overall survival were: diagnosis (lymphoma vs. leukemia; HR 0.71, 95%CI 0.58-0.87, p=0.001) and (other vs. leukemia; HR 0.72, 95%CI 0.57 - 0.92, p=0.007), age at transplant (<=20 vs >=60; HR 0.51, 95%CI 0.36 - 0.71, p<0.0001) and (21-39 vs. >=60; HR 0.57, 95% CI 0.43 - 0.77, p=0.0002), graft type (PBSC vs. BM; HR 2.0, 95%CI 1.57 - 2.5, p<0.0001), joint ABO minor MM and PBSC indicator (1 vs 0, HR 0.65, 95%CI 0.46-0.92, p= 0.014), regimen type (non-myeloablative vs. ablative; HR 0.66, 95% CI 0.53 - 0.83, p=0.0002), and transplant era (before 1998 vs 1998 - 2004; HR 1.29, 95%CI 1.03 - 1.61, p=0.03) and (after 2004 vs 1998 - 2004; HR 0.84, 95%CI 0.71 - 0.99, p=0.04). The significant covariates for NRM were: age at transplant (<=20 vs >=60; HR 0.24, 95%CI 0.15 - 0.42, p<0.0001) and (21-39 vs. >=60; HR 0.43, 95% CI 0.27 - 0.68, p=0.0003), donor relatedness (unrelated vs. HLA-identical sibling; HR 1.36, p5% CI 1.05 - 1.76, p=0.02), graft type (PBSC vs. BM; HR 1.49, 95%CI 1.1 - 2.01, p=0.01), regimen type (non-myeloablative vs. ablative; HR 0.32, 95% CI 0.23 - 0.46, p<0.0001), and transplant era (before 1998 vs 1998 - 2004; HR 1.41, 95%CI 1.06 - 1.88, p=0.02) and (after 2004 vs 1998 - 2004; HR 0.71, 95%CI 0.55 - 0.90, p=0.006).

** Variables included in CIBMTR analysis of Ratanatharathorn et al data: ABO match (matched vs. minor mismatched vs. major mismatched vs. bidirectional mismatched), age at transplantation (21-40 vs. 41-50 vs. 51-70), gender (male vs. female), performance status (<90 vs. >=90), lymphoma histology (small lymphocytic and follicular lymphoma vs. diffuse large B cell versus mantle cell), disease status prior to transplant (complete remission vs. partial remission vs. sensitive relapse vs. other relapse - ie, resistant/untreated/unknown/progressive disease), donor type

(HLA-identical sibling vs. unrelated donor), interval from diagnosis to transplant, numbers of chemotherapy regimens received prior to transplantation (<=2 lines vs. 3-6 lines vs. >6 lines), previous radiation (yes vs. no), time from last dose of rituximab to transplantation (>6 months or no prior treatment vs. <=6 months), number of prior therapy with rituximab-containing regimens, conditioning regimens (myeloablative vs. non-myeloablative), GVHD prophylaxis (ciclosporin +/- others vs. tacrolimus +/- others), donor-recipient sex match (M>M vs. M>F vs. F>M vs. F>F), donor parity (male donor vs. nulliparous female donor vs. parous female donor vs. others), donor-recipient CMV serology (-/- vs. others), year of transplant (1999-2000 vs. 2001 - 2004), and HLA match (HLA-identifcal sibling vs. well-matched vs. partially matches/mismatched unrelated). Other significant covariates are listed in the original Ratanatharathorn et al. publication.

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Variables included in CIBMTR analysis of Luger et al data: ABO match (matched vs. minor mismatched vs. major mismatched vs. bidirectional mismatched), age at transplant, gender, Karnofsky performance score (<90 vs. >=90% vs. unknown), disease (AML vs. MDS), FAB subtype at diagnosis (M0 - M2 vs. M4 - M7 vs. other/unclassified (for AML), rafractory anemia or acquired idiopathic siderblastic anemia vs. other MDS (for MDS)), therapy-related leukemia (no vs. yes vs. unknown), cytogenetics (good vs. intermediate vs. poor prognosis vs. unknown), blast percentage at transplant (<5 vs. 5-10 vs. >10% vs. unknown), duration of first CR for AML patients transplant in second CR (<6 vs. 6-12 months vs. unknown), disease status at transplant (primary induction failure vs. first CR vs >=second CR vs. relapse (for AML), treated vs. untreated (for MDS), time from remission to transplant for AML patients transplanted in first CR (<=3 vs >3 months vs unknown), type of donor (HLA-identical sibling vs. unrelated well-matched vs. unrelated partially matched vs. unrelated mismatched vs. unrelated matching unknown), donor age, donor-recipient sex match (F>M vs. other), donor-recipient CMV serology (-/- vs +/- vs. recipient + vs unknown), graft type (BM vs. PBSC), year of transplant, previous autologous transplant (no vs. yes), ATG (no vs. yes), and GVHD prophylaxis (tacrolimus + MTX +/- other vs. tacrolimus +/- other vs CSA + MTX +/- other vs CSA +/- other). Other significant covariates are listed in the original Luger et al. publication.