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ABO Mismatch Is Associated with Increased Nonrelapse Mortality after Allogeneic Hematopoietic Cell Transplantation

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We evaluated ABO associated outcomes in 1737 patients who underwent allogeneic hematopoietic cell transplantation (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, overall survival (OS) was inferior in minor MM hematopoietic cell transplantations (median 2.1 versus 6.3 years; hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.19 to 2.05; $P = .001$) in comparison with ABO-matched grafts. ABO minor MM was associated with an increase in early nonrelapse mortality (NRM) (18% versus 13%; HR, 1.48; 95% CI, 1.06 to 2.06; $P = .02$). 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 to 2.25; $P = .021$) and increased NRM (HR, 1.72; 95% CI, 1.11 to 2.68; $P = .03$) were observed in recipients of ABO minor–MM grafts. A second independent analysis of a CIBMTR data set including 5179 patients with acute myeloid leukemia and myelodysplastic syndrome identified a nonsignificant trend toward decreased OS in recipients of ABO minor–MM grafts and also found ABO major MM to be significantly associated with decreased OS (HR, 1.19; 95% CI, 1.08 to 1.31; $P < .001$) and increased NRM (HR, 1.23; 95% CI, 1.08 to 1.4; $P = .002$). ABO minor and major MM are risk factors for worse transplantation outcomes, although the associated hazards may not be uniform across different transplantation 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-transplantation treatments.

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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 cytomegalovirus (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]).

Because of microbial molecular mimicry with ABO antigens, humans are almost uniformly immunized to whichever

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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-transplantation period and has been linked to decreased overall survival (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 and July 2011. We observed that ABO minor MM was associated with a significant decrement in OS and an increase in nonrelapse mortality (NRM). To corroborate our findings, we requested the Center for International Bone and Marrow Transplant Research (CIBMTR) re-evaluate data that contributed to 2 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 among this single-institution cohort included acute myeloid leukemia (AML) and acute lymphoblastic leukemia, myelodysplastic syndrome (MDS), chronic myelogenous leukemia, primary myelofibrosis, unspecified myeloproliferative disorders, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, 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 (eg, antithymocyte globulin [ATG] or alemtuzumab).

Nonmyeloablative (NMA) regimens included those with nonablative-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 with ATG, electron beam therapy with total lymphoid irradiation and ATG) with or without additional immunosuppressive antibody treatments. Grafts were derived from bone marrow or granulocyte colony–stimulating factor (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, they 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 routinely to ensure safe blood transfusion support during the peri-transplantation 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.)

As a corroborating analysis, we reanalyzed an existing data set created by the CIBMTR to study the effect of pretransplantation rituximab on survival and graft-versus-host disease (GVHD) [18]. This cohort consisted of 435 B cell NHL 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 before HCT and 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 transplantation outcomes.

Patients — Multiple Institution (CIBMTR—Luger et al.)

We also reanalyzed an existing CIBMTR data set 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 transplantation 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* (EFS) was defined as the number of days between graft infusion and either relapse or death from any cause. Acute 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 OS and 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 HCT 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 (CI) [23].

Cumulative incidence functions with competing risks [24] were used to estimate the probabilities of relapse, NRM, NRM up to day 100, and acute GVHD grades 2 to 4 or grades 3 and 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, nonrelapse death was an event, with relapse being the competing risk. For NRM at day 100, the time horizon is 100 days after HCT—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 to 4 and grades 3 and 4, death was the competing risk in the model. Because the longest time to acute GVHD was 125 days in the Stanford patient cohort, nonevent 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 MM observed in the Stanford cohort. In 1 analysis, a mixture model was created to determine whether, for either graft type, any of the ABO MM

Table 1
Patient Characteristics

Variable	Stanford	CIBMTR (Ratanatharathorn)	CIBMTR (Luger)
No. of patients	1737	435	5179
Age, median (range), yr	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			
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			
MA	1211 (70)	197 (45)	3731 (72)
Reduced-intensity	526 (30)	238 (55)	1448 (28)
ABO			
Matched	1053 (61)	240 (59)	2608 (50)
Minor MM	297 (17)	73 (18)	1084 (21)
Major MM	309 (18)	73 (18)	977 (19)
Bidirectional MM	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)
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
Transplantation era			
1987-1997	446 (26)	0	~
1998-2004	499 (29)	435 (100)	5179 (100)
2005-July 1, 2011	792 (46)	0	0
Follow-up survivors, median (range), yr	6.0 (.3-23.7)	4.3 (.25-7.3)	1 (.09-10.7)

CML indicates chronic myeloid leukemia; PB, peripheral blood; BM, bone marrow; M, male; F, female; D, donor; neg, negative; R, recipient; pos, positive; CSA, cyclosporine; MTX, methotrexate; FK, FK506/tacrolimus.

categories were associated with survival. In this model, the interaction between graft type and ABO MM was represented by using interaction terms as covariates in the Cox regression model for overall survival [26,27]. In the second model, 8 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 pair-wise comparison of hazard ratios (HR).

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 MM, 309 (17.8%) were ABO major MM, and 78 (4.5%) were ABO bidirectionally MM. Patient characteristics within each ABO compatibility group are shown in Supplemental Table 1. Patients generally fit into 2 large categories by diagnosis: (1) leukemia group (acute myeloid and lymphoid leukemias, MDS, and chronic myelogenous leukemia), and (2) lymphoma group (NHL and CLL), 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 MA conditioning, whereas 526 (30%) received reduced-intensity conditioning. For statistical analyses, we divided treatment eras into the following groups: (1) 1986 to 1997, (2) 1998 to 2004 (before the advent of bone marrow graft plasma depletion), and (3) 2005 to July 1, 2011 (all grafts were plasma depleted).

Clinical Outcomes with ABO Minor MM 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 OS ($P = .005$) (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 MM grafts had a significantly higher risk of NRM (overall univariate HR, 1.34; 95% CI, 1.06 to 1.69; $P = .015$) (Figure 1B, Table 2). Interestingly, this significant disparity in NRM was already apparent before day 100 (HR, 1.41; 95% CI, 1.03 to 1.94; $P = .033$), but acute GVHD grade 2 to 4 was not significantly different between the 2 groups (HR, 1.6; 95% CI, .96 to 1.64; $P = .094$). As a result of increased NRM, median OS was just 2.1 years in the ABO minor MM recipients, whereas it was 6.3 years in the ABO-matched recipients (Table 2).

Graft Source Effect on ABO Minor MM 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–MM sources, were included in this retrospective analysis (Supplemental Table 2). Bone marrow grafts were highly associated with the ABO minor MM effect, with significantly decreased OS (HR, 1.7; 95% CI, 1.3 to 2.2; $P = .0002$) and EFS (HR, 1.6; 95% CI, 1.2 to 2.1; $P = .0005$) and increased NRM (HR, 1.8; 95% CI, 1.3 to 2.5; $P = .0004$). Among the bone marrow graft recipients, we also observed that the NRM at day 100 was significantly higher in recipients of ABO minor–MM grafts (HR, 2.0; 95% CI, 1.3 to 3.0; $P = .001$) and that there was an associated increase in acute GVHD grades 2 to 4 (HR, 1.6; 95% CI, 1.1 to 2.4; $P = .025$) and grades 3 and 4 (HR, 2.4; 95% CI, 1.4 to 4.1; $P = .001$). Peripheral blood grafts did not demonstrate a significant

Table 2
Patient Outcomes with ABO-Matched or ABO-MM Grafts (All Diagnoses)

Event	ABO Matched	ABO Minor MM	ABO Major MM	ABO Bidir MM
Total patients	1053	297	305	78
OS median, yr	6.3	2.1	5.87	NR
No. of events	526	167	153	32
HR (CI)	1	**1.27 (1.07-1.52)**	.98 (.82-1.18)	.8 (.56-1.5)
P value	–	**.005**	.87	.22
EFS, median, yr	2.7	1.2	2.08	7.27
No. of events	606	183	180	37
HR (CI)	1	**1.2 (1.02-1.42)**	1.02 (.86-1.21)	.8 (.57-1.11)
P value	–	**.028**	.81	.18
Relapse				
No. of events	328	89	107	20
HR (CI)	1	1.09 (.86-1.37)	1.12 (.9-1.4)	.78 (.5-1.23)
P value	–	.49	.3	.29
NRM, overall				
No. of events	278	94	73	17
HR (CI)	1	**1.34 (1.06-1.69)**	.89 (.69-1.15)	.82 (.5-1.34)
P value	–	**.015**	.38	.42
NRM, d 100				
Events at d 100	137	53	25	5
HR (CI)	1	**1.41 (1.03-1.94)**	**.62 (.4-.95)**	.48 (.2-1.18)
P value	–	**.033**	**.027**	.11
aGVHD, grade 2-4				
Events at d 125	220	72	61	14
HR (CI)	1	1.26 (.96-1.64)	.95 (.72-1.26)	.87 (.51-1.49)
P value	–	.094	.73	.6
aGVHD, grade 3-4				
Events at d 125	166	35	29	10
HR (CI)	1	1.14 (.78-1.67)	.77 (.51-1.17)	1.22 (.64-2.3)
P value	–	.49	.23	.55

Bidir indicates bidirectional; aGVHD, acute GVHD.
Significant associations are shown in bold text.

difference in the outcomes of ABO-matched and minor-MM 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 2 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 to 2.05; $P = .001$) and increased NRM (HR, 1.48; 95% CI, 1.06 to 2.06; $P = .02$) (Table 3). In the second model, pair-wise comparisons of HR with 8 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 ($P = .001$) and higher NRM ($P = .02$) than ABO-matched bone marrow. Among peripheral blood recipients, all ABO MM combinations had HR that were not significantly different than the ABO-matched group (OS, $P > .80$ and NRM, $P > .40$).

To better assess the risk of ABO MM in lymphoma patients, we analyzed an existing lymphoma patient data set 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 PBSC 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 MM on clinical outcomes. ABO status of both donor and recipient was known for 408 patients, with 240 (59%) ABO matched, 73 (18%) minor MM, 73 (18%) major MM, and 22 (5%) bidirectionally MM.

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 to 2.25; $P = .021$) (Figure 2A, Table 3). ABO minor MM also was significantly associated with increased NRM (HR, 1.72; 95% CI, 1.11 to 2.68; $P = .016$) (Figure 2C, Table 3). ABO MM did not significantly associate with relapse, acute GVHD grades 2 to 4 or grades 3 and 4, or chronic GVHD (data not shown).

To address ABO MM effects in patients with myeloid diseases treated at multiple institutions, we also re-evaluated an existing CIBMTR data set addressing the outcome of 5179 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 to 1.31; $P < .001$) and increased NRM (HR, 1.23; 95% CI, 1.08 to 1.40; $P = .002$) (Figure 2B,D). ABO minor MM was not significantly associated with changes in OS (HR, 1.06; 95% CI, .97 to 1.16; $P = .24$) or NRM (HR, 1.07; 95% CI, .94 to 1.21; $P = .33$).

DISCUSSION

This study describes the effect of ABO MM on outcomes in patients undergoing related and unrelated donor allo-HCT for all indications at a single institution (Stanford University), and in 2 published CIBMTR registry studies that did not previously account for ABO MM in multivariate models of

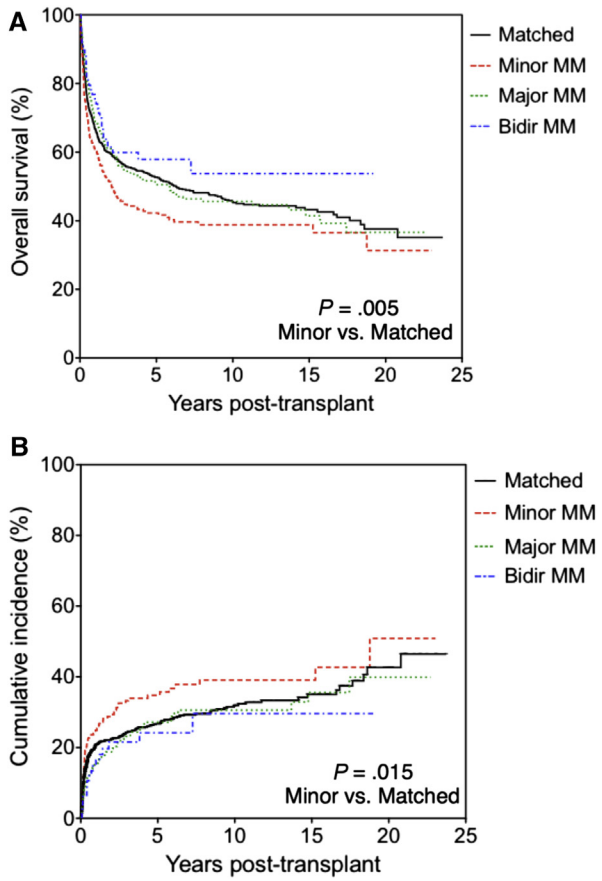

Figure 1. Recipient survival when donor was ABO matched, minor MM, major MM, or bidirectionally MM. Recipients receiving minor-MM grafts experienced a significant overall survival impairment compared with those receiving ABO-matched grafts ($P = .005$) (A). Cumulative incidence of NRM was increased in recipients of ABO minor MM grafts compared with recipients of ABO-matched grafts ($P = .015$) (B).

hazards for NRM and OS [18,19]. In the Stanford cohort of 1737 patients who underwent transplantation between 1986 and 2011, we identified a significant impairment in OS (univariate HR, 1.27; 95% CI, 1.07 to 1.52; $P = .005$; multivariate HR, 1.56; 95% CI, 1.19 to 2.05; $P = .001$) in patients receiving ABO minor–MM grafts, whereas other forms of ABO MM were not significantly associated with outcome (Figure 1A; Tables 2 and 3). The survival decrement in recipients of ABO minor–MM grafts is attributable to increased NRM (univariate HR, 1.34; 95% CI, 1.06 to 1.69; $P = .015$; multivariate HR, 1.48; 95% CI, 1.06 to 2.06; $P = .02$), with risk of mortality evident before day 100 after transplantation. A nonsignificant trend toward increased acute GVHD grades 2 to 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 adoptively transferred into recipients [28]. In recipients of ABO minor–MM bone marrow grafts, an increased risk of acute GVHD was observed (HR, 1.6; 95% CI, 1.1 to 2.4; $P = .025$) (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 to 2.68; $P = .02$) and decreased OS (multivariate HR, 1.55; 95% CI, 1.07 to 2.25; $P = .021$) with ABO minor–MM grafts in a relatively homogeneous cohort of lymphoma patients, all of whom received PBSC grafts (Figure 2A,C), suggesting the attributable risks of this form of ABO incompatibility may not exclusively be present with marrow grafts. It is likely that host features interact with adoptively transferred lymphocytes from ABO MM 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-transplantation immune suppression tapers. It is also possible that lymphoma patients, being lymphopenic from lymphotoxic therapies for their primary disease, may experience increased post-transplantation 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 before adoptive lymphocyte transfer.

Although 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 who underwent transplantation at 223 centers in 37 different countries [19] The Luger et al. [19] study included only patients with AML and MDS, but with a mixture of bone marrow and PBSC grafts (2333 versus 2846) and MA and RIC/NMA conditioning (3731 versus 1448). The reasons for the difference in the impact of ABO minor–MM grafts in this study in comparison with the other studies remain unclear, but it is possible that the relatively low OS in this cohort (34% for myeloablated recipients, 33% for reduced-intensity conditioning, and 26% for NMA conditioning) affected 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 (Figure 2B,D).

Watz et al. recently reported an analysis of transplantation 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 1 month of transplantation [29]. In their study, 6 patients out of 66 with ABO minor–MM grafts met these criteria and their survival was 0% versus 61% in patients without PLS ($P < .001$); however, deaths were more frequently associated with relapse than NRM, and the generalizability of these data are unclear because 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 after transplantation, 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

Table 3
Multivariate Cox Regression Analysis of ABO MM Effect on OS and NRM

Event	ABO Matched	ABO Minor MM	ABO Major MM	ABO Bidir MM
OS, Stanford*				
No. evaluable	1049	293	309	78
HR (CI)	1	**1.56 (1.19-2.05)**	1.02 (.85-1.23)	.87 (.61-1.26)
P value	–	**.001**	.82	.82
OS, CIBMTR (Ratanatharathorn)†				
No. evaluable	240	73	73	22
HR (CI)	1	**1.55 (1.07-2.25)**	.86 (.57-1.31)	.94 (.37-2.39)
P value	–	**.021**	.49	.91
OS, CIBMTR (Luger)‡				
No. evaluable	2540	1065	955	308
HR (CI)	1	1.06 (.97-1.16)	**1.19 (1.08-1.31)**	1.13 (.97-1.31)
P value	–	.24	**<.001**	.11
NRM, Stanford*				
No. evaluable	1049	293	309	78
HR (CI)	1	**1.48 (1.06-2.06)**	.91 (.7-1.18)	.94 (.57-1.55)
P value	–	**.02**	.47	.81
NRM, CIBMTR (Ratanatharathorn)†				
No. evaluable	240	73	73	22
HR (CI)	1	**1.72 (1.11-2.68)**	.87 (.52-1.46)	1.42 (.69-2.9)
P value	–	**.02**	.6	.34
NRM, CIBMTR (Luger)‡				
No. evaluable	2540	1065	955	308
HR (CI)	1	1.07 (.94-1.21)	**1.23 (1.08-1.4)**	1.11 (.9-1.36)
P value	–	.33	**.002**	.35

Significant associations are shown in bold text.

* Variables included in the model are: ABO match (matched versus minor MM versus major MM versus bidirectional MM), diagnosis category (leukemia versus lymphoma versus other), age at transplantation (≤20, 21 to 39, 40 to 59, ≥60), recipient gender (male versus female), donor relatedness (HLA-identical sibling versus unrelated), graft type (PBSC versus bone marrow), indicator of joint ABO minor MM and PBSC, regimen type (MA versus NMA), transplantation era (before 1998 versus 1998 to 2004 versus after 2004). The significant covariates for overall survival were: diagnosis (lymphoma versus leukemia; HR, .71; 95% CI, .58 to .87; $P = .001$) and (other versus leukemia; HR, .72; 95% CI, .57 to .92; $P = .007$), age at transplantation (≤20 versus ≥60; HR, .51; 95% CI, .36 to .71; $P < .0001$) and (21 to 39 versus ≥60; HR, .57; 95% CI, .43 to .77; $P = .0002$), graft type (PBSC versus BM; HR, 2.0; 95% CI, 1.57 to 2.5; $P < .0001$), joint ABO minor MM and PBSC indicator (1 versus 0, HR, .65; 95% CI, .46 to .92; $P = .014$), regimen type (NMA versus MA; HR, .66; 95% CI, .53 to .83; $P = .0002$), and transplantation era (before 1998 versus 1998 to 2004; HR, 1.29; 95% CI, 1.03 to 1.61; $P = .03$) and (after 2004 versus 1998 to 2004; HR, .84; 95% CI, .71 to .99; $P = .04$). The significant covariates for NRM were age at transplantation (≤20 versus ≥60; HR, .24; 95% CI, .15 to .42; $P < .0001$) and (21 to 39 versus ≥60; HR, .43; 95% CI, .27 to .68; $P = .0003$), donor relatedness (unrelated versus HLA-identical sibling; HR, 1.36; 95% CI, 1.05 to 1.76; $P = .02$), graft type (PBSC versus BM; HR, 1.49; 95% CI, 1.1 to 2.01; $P = .01$), regimen type (NMA versus MA; HR, .32; 95% CI, .23 to .46; $P < .0001$), and transplantation era (before 1998 versus 1998 to 2004; HR, 1.41; 95% CI, 1.06 to 1.88; $P = .02$) and (after 2004 versus 1998 to 2004; HR, .71; 95% CI, .55 to .90; $P = .006$).

† Variables included in CIBMTR analysis of Ratanatharathorn et al. data: ABO match (matched versus minor MM versus major MM versus bidirectional MM), age at transplantation (21 to 40 versus 41 to 50 versus 51 to 70), gender (male versus female), performance status (<90 versus ≥90), lymphoma histology (small lymphocytic and follicular lymphoma versus diffuse large B cell versus mantle cell), disease status before transplantation (complete remission versus partial remission versus sensitive relapse versus other relapse, ie, resistant/untreated/unknown/progressive disease), donor type (HLA-identical sibling versus unrelated donor), interval from diagnosis to transplantation, numbers of chemotherapy regimens received before transplantation (≤2 lines versus 3 to 6 lines versus >6 lines), previous radiation (yes versus no), time from last dose of rituximab to transplantation (>6 months or no prior treatment versus ≤6 months), number of prior therapy with rituximab-containing regimens, conditioning regimens (MA versus NMA), GVHD prophylaxis (cyclosporin ± others versus tacrolimus ± others), donor-recipient sex match (M>M versus M>F versus F>M versus F>F), donor parity (male donor versus nulliparous female donor versus parous female donor versus others), donor-recipient CMV serology (−/− versus others), year of transplantation (1999 to 2000 versus 2001 to 2004), and HLA match (HLA-identical sibling versus well-matched versus partially matches/MM unrelated). Other significant covariates are listed in the original Ratanatharathorn et al. publication.

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

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 before transplantation to ablate adoptively transferred B lymphocytes. We attempted to evaluate the Stanford data set for possible beneficial effect from the administration of rituximab within 6 months before 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–MM patients with NHL and CLL patients who received rituximab within 6 months before allo-HCT, with improved OS (HR, .4; 95% CI, .2 to .9; $P = .02$) and decreased NRM (HR, .3; 95% CI, .1 to .9; $P = .03$) in comparison with 19 NHL/CLL ABO minor–MM 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–MM PBSC grafts longer than 6 months after the last dose of rituximab (HR, 1.6 versus

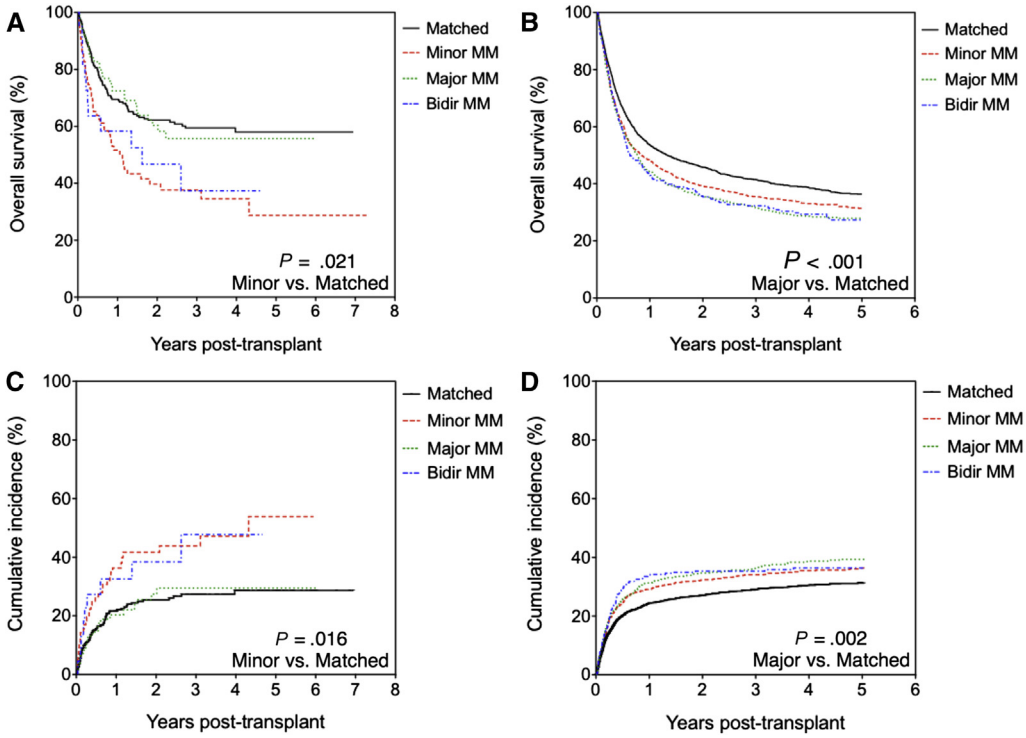

Figure 2. CIBMTR analysis of overall survival and cumulative incidence of NRM in patients receiving ABO-matched, minor MM, major MM, or bidirectionally (Bidir) MM hematopoietic allografts for lymphoma (A and C; data from Ratanatharathorn et al. [18] evaluated for ABO effect) or AML/MDS (B and D; data from Luger et al. [19] evaluated for ABO effect).

ABO matched grafts; 95% CI, 1.03 to 2.5; $P = .037$), whereas the survival of 29 patients receiving ABO minor–MM 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, .75 to 2.79; $P = .27$). A complete analysis of these outcomes in the Stanford and CIBMTR (Ratanatharathorn et al. [18]) data sets 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 HR. 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 et al. 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%, $P = .03$) and decreased 3-year OS (17% versus 73%, $P = .002$) [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 or additional blood product support and iron overload toxicity, or the finding may be spurious given the small sample size. Again, though, routine post-transplantation measurement of anti-ABO antibodies and capture of such data in transplantation 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 1 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 2 of the 3 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 transplantation 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-MM donor, when the option exists.

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SUPPLEMENTARY DATA

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