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The Impact of Donor Type and ABO Incompatibility on Transfusion Requirements after Nonmyeloablative Hematopoietic Cell Transplantation (HCT)

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Summary

We retrospectively analyzed transfusion requirements within the first 100 days among allogeneic hematopoietic cell transplantation (HCT) recipients with hematological malignancies given either myeloablative (n=1353) or nonmyeloablative conditioning (n=503). We confirmed that myeloablative recipients required more platelet and red blood cell (RBC) transfusions than nonmyeloablative recipients (both $P < 0.0001$). Myeloablative patients given peripheral blood stem cells required less platelet transfusions ($P < 0.0001$) than those given marrow while RBC transfusion requirements did not differ significantly. Subsequent analyses were restricted to nonmyeloablative recipients. Related recipients required less platelet and RBC transfusions compared to unrelated recipients ($P < 0.0001$ for both), with comparable median numbers of transfused units. Major/bidirectionally ABO-mismatched recipients required more RBC transfusions than ABO-matched recipients ($P = 0.006$). Rates of graft rejection/failure, grades II–IV acute and chronic graft-versus-host-disease (GVHD), 2-year relapse, 3-year survivals and non-relapse mortality were comparable among ABO-matched, minor-mismatched, and major/bidirectionally mismatched recipients ($P = 0.93, 0.72, 0.57, 0.36, 0.17$ and 0.79 , respectively). Times to disappearance of anti-donor IgG and IgM isohemagglutinins among major/bidirectionally ABO-mismatched recipients were affected by magnitude of pre-HCT titres ($P < 0.001$ for both) but not GVHD ($P = 0.71$ and 0.78 , respectively). In conclusion, nonmyeloablative recipients required fewer platelet and RBC transfusions and among them, both unrelated and major/bidirectionally ABO-mismatched recipients required more RBC transfusions. ABO incompatibility did not affect nonmyeloablative HCT outcomes.

Keywords

nonmyeloablative conditioning; allogeneic HCT; ABO-incompatibility; transfusion

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for many patients with hematological malignancies. Historically, high-dose conditioning regimens have been used with the dual aims of disease eradication and host immunosuppression for acceptance of the allografts (Little & Storb, 2002). Over the past several years, we have used a truly nonmyeloablative conditioning regimen in order to reduce the morbidity and mortality associated with high-intensity regimens and extend HCT to include older patients and those with comorbidities. The regimen consisted of 2 Gy total body irradiation (TBI) with or without 90 mg/m² fludarabine (FLU), and post-grafting immunosuppression with mycophenolate mofetil (MMF) and either cyclosporine (CSP) or FK506 (Carella *et al*, 2000; McSweeney *et al*, 2001). An early study involving small numbers of patients showed reduced transfusion requirements among nonmyeloablative compared to myeloablative recipients of human leucocyte antigen (HLA)-identical sibling HCT (Weissinger *et al*, 2001). Other studies involving myeloablative HCT recipients showed that fewer transfusions were required for recipients of related compared to unrelated grafts (Anasetti *et al*, 1989; Mielcarek *et al*, 2000; Zaucha *et al*, 2002; Sorror *et al*, 2004). Whether or not HCT from unrelated donors affected transfusion requirements in the nonmyeloablative HCT setting remained to be evaluated.

Major ABO incompatibility between donors and recipients has been associated with delayed red blood cell recovery, transient pure red cell aplasia and, thereby, prolonged need for red blood cell (RBC) transfusions in the high-dose HCT setting (Bolan *et al*, 2001a, b; Worel *et al*, 2003; Griffith *et al*, 2005). Results on effects of ABO compatibility on HCT outcomes were not consistent, with some studies suggesting that ABO incompatibility increased overall mortality, graft-versus-host disease (GVHD) and graft rejection/failure following both nonmyeloablative and myeloablative HCT (Benjamin *et al*, 1999; Stussi *et al*, 2001; Stussi *et al*, 2002; Worel *et al*, 2003; Remberger *et al*, 2007), others suggesting a lower risk of relapse but little effect on overall survival, and yet others seeing no effects on HCT outcomes (Klump *et al*, 2006; Mielcarek *et al*, 2000; Mehta *et al*, 2002; Goldman *et al*, 2003; Seebach *et al*, 2005). Only limited information has been available on the impacts of ABO incompatibility on both RBC and platelet transfusion requirements in the nonmyeloablative HCT setting (Weissinger *et al*, 2001; Zaucha *et al*, 2002; Badros *et al*, 2002; Baron *et al*, 2006).

Here, we retrospectively analyzed RBC and platelet transfusion needs among a larger number of patients with hematological malignancies who received nonmyeloablative conditioning. We compared RBC and platelet transfusion needs among patients given grafts from related versus unrelated donors, and analyzed the effect of ABO incompatibility on transfusion requirements and nonmyeloablative HCT outcomes. In addition, we compared transfusion needs after nonmyeloablative and myeloablative HCT among concurrently transplanted patients.

Materials and Methods

Patients

The study analyzed RBC and platelet transfusion needs during the first 100 days among 1,856 consecutive patients with hematological malignancies who received either HLA-matched related or unrelated HCT after nonmyeloablative (n=503), or myeloablative (n=1353) conditioning regimens between December 1997 and February 2008 at the Fred Hutchinson Cancer Research Center (FHCRC) (Table I). Patients and donors were matched for HLA-A, -B, and -C antigens by either intermediate resolution DNA typing (to a level at

least as sensitive as serology) or high-resolution techniques. HLA matching for HLA-DRB1 and -DQB1 was done at the allele level (Petersdorf *et al*, 1998).

The nonmyeloablative regimen consisted of 2 Gy TBI with or without fludarabine, 30mg/m²/day from days -4 to -2, and postgrafting immunosuppression with MMF and CSP or FK506. Myeloablative conditioning consisted of busulfan and cyclophosphamide, or 12–14.4 Gy fractionated TBI and cyclophosphamide. Post-grafting immunosuppression in myeloablative recipients consisted of methotrexate (MTX) or MMF plus CSP or FK506. Nonmyeloablative protocols were offered to patients who were either > 50 years old or, if < 50 years old, had significant pre-existing medical problems or had preceding high-dose HCT.

ABO-incompatible transplants

ABO-incompatible transplantations were performed according to FHCRC standard practice guidelines (Rowley *et al*, 2000; Mielcarek *et al*, 2000). Minor ABO- mismatches were characterized by the presence of anti-recipient isohemagglutinins in donors, e.g., O-type donors and A-, B- or AB-type recipients; major ABO-mismatches included the presence of anti-donor isohemagglutinins in recipients, e.g., A-, B- or AB-type donors and O-type recipients; bidirectionally ABO- mismatches were characterized by the combination of major and minor ABO-mismatches, e.g., A-type donors and B-type recipients, or B-type donors and A-type recipients.

Standard practice guidelines (Rowley *et al*, 2000) for management of major ABO incompatibility at FHCRC were as follows: if marrow served as the source of stem cells, RBC depletion was performed in related transplants, and plasma exchange using donor type plasma was performed in recipients of unrelated transplants whenever anti-donor isohemagglutinins titres were greater than 1:16. If granulocyte colony-stimulating factor “mobilized” peripheral blood mononuclear cells served as the stem cell source, the product was infused without manipulation if the calculated RBC volume was less than 10 ml.

Transfusion policies

Platelet support was given when platelet counts were less than $10 \times 10^9/l$ in the outpatient setting and less than $20 \times 10^9/l$ in the inpatient setting or when patients had signs of bleeding. Patients received random donor platelets unless they developed refractoriness. Random platelets were either whole-blood pooled random platelets or random single-donor apheresis platelets. Before transplantation, all patients received leucocyte-reduced platelets. After transplantation, leucocyte reduction was no longer required. Packed RBCs were transfused when hematocrits were less than 26% or when patients were symptomatic.

Volume-reduced platelets were used to minimize the amount of isohemagglutinins in ABO-mismatched platelet transfusions. For patients with minor ABO mismatches, post-transplantation platelet transfusions were of recipient (or AB) type, and RBC transfusions were O-type; for patients with major ABO-mismatches and bidirectional mismatches, post-transplantation platelet transfusions were of donor or AB-type as first choice, and RBC transfusions were O-type. Plasma was depleted when O-group platelets were used for A-, B- or AB-group recipients. All transfusions were irradiated. IgG and IgM isohemagglutinins titres were measured in recipients before transplant and followed weekly after transplant until titres were undetectable for two consecutive weeks (Buckner *et al*, 1978). Once hemagglutinin titres were undetectable, RBC transfusions were switched to donor type RBCs. If bidirectionally ABO incompatibility was present, plasma exchange, if indicated, was performed with pooled AB plasma. Post-transplant RBC transfusion guidelines in this

group of patients were according to major ABO-mismatched transplants. Erythropoietin was not used for the treatment of complications associated with ABO-incompatible HCT.

Laboratory tests

Complete blood counts were obtained frequently as indicated; serum lactate dehydrogenase and total bilirubin levels were obtained three times per week. Haptoglobin and direct anti-globulin testing were not performed routinely but performed if clinically indicated. The results of serological tests performed at the Puget Sound Blood Center (Seattle, WA, USA) were obtained retrospectively from transfusion records and patient charts.

Statistical analysis

Summary statistics such as median and ranges were presented. Unadjusted comparisons of proportions of patients requiring platelet and RBC transfusion support during the first 100 days after transplant were made between recipients of nonmyeloablative transplants and myeloablative transplants, and different subgroups among nonmyeloablative HCT recipients using χ^2 tests. Among subjects who received at least one transfusion, the median number of days and units of platelet and RBC transfusions received were compared between the same groups using a Wilcoxon ranksum test. Cumulative incidences of the probability of disappearance of IgG and IgM isohemagglutinin titres, acute and chronic GVHD, graft rejection and relapse were calculated, treating death as a competing risk event for each outcome (Kalbfleisch & Prentice, 1980). Survival curves were evaluated using the method of Kaplan and Meier. Univariate comparisons between cumulative incidence and survival curves were made using a logrank test. Cox proportional hazards models were used to evaluate potential multivariate effects of risk factors on disappearance of IgG and IgM isohemagglutinin titres and to evaluate hazard ratios (HR) and associated 95% confidence intervals (CI). All reported p-values are two-sided, with a significance level of 0.05.

Results

Pre-transplantation patient characteristics

The characteristics of the patients treated with either myeloablative or nonmyeloablative conditioning are listed in Table I. The median age of patients given nonmyeloablative conditioning was 56.2 years compared to 42 years for myeloablative patients ($P < 0.0001$). Diagnoses among nonmyeloablative patients mainly included non-Hodgkin and Hodgkin lymphomas, acute and chronic leukemias, and multiple myeloma (MM), while those in myeloablative patients were mainly acute leukemia (AL), chronic myeloid leukemia (CML) and myelodysplasia (MDS). Among the 503 nonmyeloablative recipients, 52.7% had grafts from related donors and 47.3% had grafts from unrelated donors; 58.1% had grafts from ABO-compatible donors and 41.9% from ABO-incompatible donors, including 20.3% minor ABO-mismatches and 21.7% major plus bidirectionally ABO-mismatches. Among the 1,353 myeloablative recipients, 52.9% and 47.1%, respectively, had grafts from related and unrelated donors; 51.2%, 22.1% and 26.7%, respectively, had grafts from ABO-matched, minor ABO-mismatched and major plus bidirectionally ABO-mismatched donors.

Comparing transfusion requirements in myeloablative and nonmyeloablative recipients

Virtually all myeloablative patients received platelet (99%) and RBC (96%) transfusions compared to 36% and 75% of nonmyeloablative patients, respectively ($P < 0.0001$ for both, Table II). Both platelets and RBC transfusion requirements declined over the 100-day time period, with the majority of transfusions given within the first 25 days. Among myeloablative patients, recipients of peripheral blood stem cells (PBSC) (n=816) required fewer days and units of platelet transfusions, with medians of 4 days (range, 0–90) and 24

units (range, 0–920), respectively, compared to recipients of bone marrow (BM, $n=533$), with medians of 8 days (range, 0–83) and 44 units (range, 0–681), respectively ($P < 0.0001$ for both), while RBC transfusion units and days did not differ significantly ($P = 0.34$ and 0.06 , respectively). Thirty five percent and 74% of nonmyeloablative PBSC recipients ($n = 492$) required platelet and RBC transfusions compared to 99% and 97% myeloablative PBSC recipients, respectively ($P < 0.0001$ for both). Nonmyeloablative PBSC recipients also required fewer days and units of both platelet and RBC transfusions compared to myeloablative PBSC recipients ($P = 0.0003$ for both days and units of platelets transfusions, and $P = 0.02$ and 0.01 for days and units of RBC transfusions, respectively)

Among those given transfusions, nonmyeloablative patients required fewer days of transfusion support, with a median of 3 days for platelets and 4 days for RBCs compared to medians of 6 days and 4 days, respectively, for myeloablative patients (Fig. 1A, $P < 0.0001$ and $P = 0.0007$, respectively). Transfused nonmyeloablative recipients required overall less platelet and RBC units than myeloablative patients (Fig. 1B and C), with medians of 18 platelet units (range, 4–538) and 7 RBC units (range, 1–41), compared to medians of 34 platelet units (range, 4–920) and 8 RBC units (range, 1–127), respectively ($P < 0.0001$ and $P = 0.0002$, respectively). Furthermore, after adjusting for underlying diseases (AL, MDS, and CML vs. lymphoma, MM, and chronic lymphoblastic leukaemia), the myeloablative cohort still required overall more days ($P = 0.001$ and 0.068 , respectively) and more units ($P = 0.005$ and 0.009 , respectively) of platelets and RBC transfusions.

Transfusion requirements among nonmyeloablative HCT recipients

Related vs. unrelated grafts—Twenty nine percent and 68% of related recipients required platelet and RBC transfusions, respectively, compared to 45% and 82% of unrelated recipients respectively (Table II, $P < 0.0001$ for both). Both related and unrelated recipients required a median of 3 days of platelet transfusions ($P = 0.43$); however, related recipients required a median of 3 days of RBC transfusions compared to 5 days for unrelated recipients (Fig. 2A, $P = 0.012$). The overall numbers of platelet and RBC units transfused were not significantly different among transfused related versus unrelated recipients (Fig. 2B and C), with medians of 16 (range, 4–538) versus 22 (range, 4–258) platelet units ($P = 0.48$), and medians of 6 (range, 1–41) versus 8 (range, 1–40) RBC units ($P = 0.063$).

ABO-matched vs. ABO-mismatched recipients—Compared to major/bidirectionally-ABO- mismatched recipients, ABO-matched recipients required slightly fewer platelet (34% versus 42%, $P = 0.14$) and significantly less RBC (70% versus 83%, $p=0.006$) transfusions (Table II). There were no statistically significant differences between ABO-matched and minor ABO-mismatched recipients. Among patients who required transfusions, the median days for platelet transfusions were 3, 2, and 3.5 for ABO-matched, minor ABO-mismatched, and major/bidirectionally ABO-mismatched patients, respectively. But the differences between ABO-matched patients and ABO- mismatched patients were not statistically significant ($P = 0.55$ and 0.75 for minor and major/bidirectional ABO mismatched, respectively). The median numbers of days for RBC transfusions were 3 days for ABO-matched and 3.5 days for minor ABO-mismatched recipients compared to medians of 5 days for major/ bidirectionally ABO-mismatched recipients ($P = 0.004$ and 0.026 respectively, [Fig. 3A]). Furthermore, major/bidirectionally ABO-mismatched recipients required a median of 19 (range, 4–538) platelet units compared to medians of 18 (range, 4–258) and 12 (range, 4–158) units ($P = 0.93$ and 0.40 , respectively) for ABO-matched and minor ABO-mismatched recipients (Fig. 3B). Medians of 6 units of RBC were given in ABO-matched (range, 1–38) and minor ABO-mismatched (range, 1–40) compared to 9 units (range, 1–41) in major/bidirectionally ABO-mismatched recipients, respectively ($P = 0.026$ and 0.0095 , respectively [Fig. 3C]).

Among major/bidirectionally ABO-mismatched recipients, unrelated grafts resulted in trends for increased platelet and RBC transfusion needs (46% and 86%, respectively), compared to related grafts (38% and 80%, respectively, Table II) with $P = 0.41$ and 0.37 for RBC and platelets, respectively.

Times to disappearance of anti-donor isohemagglutinin titres in ABO-mismatched recipients—Among the 109 nonmyeloablative patients receiving major/bidirectionally ABO-mismatched grafts, 98 had evaluable data on duration of persistence of anti-donor IgG and IgM isohemagglutinin titres after HCT. Among these, 93 subjects eventually reached disappearance of titres, and 9 had not yet reached disappearance of titres at their last follow up and thus were censored. Fig. 4 shows the cumulative incidence of disappearance of IgG and IgM titres with median days to disappearance of 48 and 47 days, respectively. There were no significant differences between recipients of related compared to unrelated grafts ($P = 0.40$ and 0.35 , for IgG and IgM, respectively).

A Cox regression model was used to more precisely examine how the magnitude of anti-donor isohemagglutinin titres at HCT affected the times to disappearance of titres after HCT. To this end, the quartiles of pre-HCT titres were included as categorical covariates. Higher pre-transplantation IgG and IgM titres were statistically significantly associated with longer persistence of titres ($P < 0.001$ for both, Fig. 5). We also evaluated whether the impact of donor type on the hazards of titre disappearance was impacted by adjustment for pre-HCT titres. No significant differences were detected between related and unrelated grafts ($P = 0.957$ and 0.743 for IgG and IgM, respectively), though impact of pre-HCT titres remained significant.

We had suggested that graft-versus-plasma cell effects influenced the clearance rate of isohemagglutinins titres in the myeloablative setting (Mielcarek *et al*, 2000). In Cox regression analysis adjusted for pre-HCT titre levels, we found no statistically significant differences in the likelihood of reaching titre endpoints among nonmyeloablative recipients of major/bidirectionally ABO-mismatched grafts who experienced grades II–IV compared to those with grades 0–1 acute GVHD ($P = 0.901$ and 0.858 for IgG and IgM, respectively).

ABO-incompatibility and HCT outcomes—Cumulative incidences of graft rejection/failure among ABO-matched, minor-mismatched, and major/bidirectionally-mismatched patients were comparable at 4.8%, 3.9% and 5.0%, respectively (Table III, $P = 0.93$). Similarly, no statistically significant differences were detected in incidences of grades II–IV acute GVHD and extensive chronic GVHD as stratified by degree of ABO-matching/mismatching (Table III, $P = 0.72$ and 0.57 , respectively). Also, the cumulative incidences of relapse of underlying malignancies at 2 years after HCT did not differ between the three patient groups ($P = 0.36$). Finally, 3-year survival (Fig. 6, $P = 0.17$) and non-relapse mortality (Table III, $P = 0.79$) rates among nonmyeloablative patients, as stratified by ABO-matching/mismatching, were not statistically significantly different among the groups.

Discussion

The present study included almost 1,900 concurrently transplanted patients, and confirmed earlier findings by us (Weissinger *et al*, 2001) and others (Ivanov *et al*, 2004; Le Blanc *et al*, 2004) that patients given nonmyeloablative conditioning before allogeneic HCT required significantly fewer platelet and RBC transfusions than myeloablative recipients. Specifically, 64% nonmyeloablative patients never needed platelet transfusions, and 24% did not require RBC transfusions compared to 1% and 4% of myeloablative patients, respectively. Given both the larger proportion of marrow grafts among myeloablative recipients and their greater transfusion requirements compared to PBSC grafts, we repeated

the comparison with the focus on PBSC recipients and found the findings did not change. Further, among transfused nonmyeloablative patients, the numbers of platelet and RBC units were significantly lower than among their myeloablative counterparts. The differences in underlying disease diagnoses did not affect transfusion requirement between the two groups. There were at least two reasons for the decreased transfusion requirements. First, unlike a myeloablative regimen, the combination of 2 Gy TBI $\pm$ fludarabine did not cause major marrow damage, and host hematopoiesis continued until gradually being replaced by donor hematopoiesis. Second, other reasons for increased transfusion needs in myeloablative patients, such as gastrointestinal damage, veno-occlusive disease of the liver, diffuse alveolar hemorrhage, regimen-related hemorrhagic cystitis, and bacterial sepsis, were either absent or significantly decreased in nonmyeloablative patients (Hogan *et al*, 2004; Junghanss *et al*, 2002; Chien *et al*, 2005; Sorrow *et al*, 2004; Diaconescu *et al*, 2004). The decreased transfusion requirements among nonmyeloablative recipients were seen even though patients were older, more heavily pretreated, and generally in worse medical condition.

Among patients given nonmyeloablative conditioning, those with unrelated grafts required more days of RBC but not platelet transfusions, while overall numbers of transfused platelet and RBC units were not statistically different between the two cohorts. Previous findings in myeloablative recipients included both increased RBC and platelet requirements after unrelated grafts, which were thought to be due to accelerated elimination of host hematopoiesis and more frequent, more severe and earlier-onset of acute GVHD resulting from greater non-HLA histocompatibility disparities in the unrelated setting (Mielcarek *et al*, 2000). Perhaps the almost uniform use of PBSC grafts among current nonmyeloablative recipients helped to minimize these previously observed differences.

Unsurprisingly, and consistent with previous reports in both reduced-intensity conditioning (Zauch *et al*, 2002; Worel *et al*, 2003; Canals *et al*, 2004) and myeloablative settings (Mielcarek *et al*, 2000; Seebach *et al*, 2005), patients with major/bidirectionally ABO-incompatibilities required more RBC transfusions than ABO-compatible and minor ABO-mismatched recipients. This resulted from extended persistence of host plasma cells generating anti-donor isohemagglutinins (Griffith *et al*, 2005). Among major ABO-incompatible recipients, the extent of RBC support depended on the magnitude of anti-donor isohemagglutinins titres at the time of HCT, which was a major factor in the duration of persistence of such titres. Median times for disappearances of titres among recipients of related and unrelated grafts were comparable, at 47 and 48 days, respectively, for IgM and IgG. The higher platelet transfusion requirements in major/bidirectionally ABO-mismatched recipients could be explained by the reported variable expression of group A and group B substances on platelets (Curtis & McFarland, 2009), which might make donor platelets targets for the same isohemagglutinins that lysed donor RBC.

A previous study (Mielcarek *et al*, 2000) in 383 myeloablative recipients had suggested that graft-versus-plasma cell effects determined the tempo of disappearance of anti-donor titres; however, a correlation between GVHD and disappearance of titres was not found in the current nonmyeloablative patients. The difference in results might have been due to smaller current patient numbers, differences in GVHD prophylaxis, and higher rates of severe GVHD among myeloablative patients (Mielcarek *et al*, 2000).

Consistent with our previous study of 1,676 myeloablative recipients (Mielcarek *et al*, 2000) and two smaller studies in patients given nonmyeloablative, reduced-intensity or myeloablative conditioning regimens by Canals *et al*. and Goldman *et al*. (Zauch *et al*, 2002; Goldman *et al*, 2003; Worel *et al*, 2003; Canals *et al*, 2004; Resnick *et al*, 2008), the current study of nonmyeloablative recipients failed to show significant associations between

ABO-mismatching and HCT outcomes, including rates of engraftment, acute and chronic GVHD, disease relapse, survival and non-relapse mortality. This did not surprise us given that group A and B antigens have not been considered bona fide transplantation antigens. In contrast, studies reported by Worel et al and Resnick et al. (Worel *et al*, 2003; Resnick *et al*, 2008; Zaucha *et al*, 2002) indicated increases in non-relapse mortality with major ABO-mismatched grafts, which the latter authors interpreted to be due to increased GVHD-related mortality. Variable associations between ABO-mismatching and HCT outcomes have been reported in myeloablative HCT settings. A Center for International Blood and Marrow Transplant Research analysis (Seebach *et al*, 2005), while detecting no differences in survival, showed an increase in grades III-IV acute GVHD in bidirectionally ABO-mismatched recipients. Stussi et al., (2002), on the other hand, reported lower overall survival in a small group of recipients given bidirectionally ABO-mismatched grafts. The authors attributed their findings to synergistic adverse effects of both major and minor ABO-incompatibilities (Stussi *et al*, 2002). An earlier study in patients given T-cell-depleted grafts reported an increase in grades II-IV acute GVHD associated with minor ABO-mismatched but not bidirectionally-mismatched grafts (Keever-Taylor *et al*, 2001). The authors stated that "the mechanism behind the association of minor ABO disparity with acute GVHD was not clear." A decreased disease relapse rate in ABO-mismatched patients with AML in first complete remission and improved event-free survival were reported by Mehta et al. (2002), with no detection of differences in acute or chronic GVHD. The authors attributed their findings to enhanced graft-versus-leukemia effects by immune reactions directed at ABO-mismatched grafts. Finally, Remberger et al. (2007) observed increased rejections among ABO-mismatched recipients, which they thought were due to binding of anti-donor A/B antibodies to A/B antigens absorbed on neutrophils or their precursors, which eventually led to their elimination or suppression. The reasons for the differences in outcomes among the various reports were not obvious, but might have to do with differences in conditioning regimens, GVHD prophylaxis, multi-centre effects, and relatively small patient numbers in some of the studies.

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Fig. 1. Comparisons of platelet and RBC (red blood cells) transfusions between nonmyeloablative and myeloablative HCT patients who received at least one transfusion Nonmyeloablative recipients required less days of transfusion (A) and units of both platelets (B) and RBC (C).

Fig. 2. Comparison of platelet and RBC transfusions among related and unrelated nonmyeloablative patients who received at least one transfusion

Recipients given related grafts required less days of RBC transfusions (A). The days of platelet and the units of transfused platelets (B) and RBC (C) were not significantly different between the two groups.

Fig. 3. Influence of ABO-incompatibility on Platelets and RBC transfusion requirements among nonmyeloablative HCT patients who received at least one transfusion

(A) Recipients given major/bidirectionally ABO-mismatched grafts required more days of RBC transfusion than recipients given ABO-matched or minor mismatched grafts ($P=0.004$ and 0.026 , respectively); (B) No significant difference between platelet units required by ABO-matched and -mismatched HCT recipients; (C) major/bidirectionally ABO-mismatched HCT required significantly more RBC transfusion units than the other two groups. *Reference group for comparisons.

Fig. 4. Patients with nonmyeloablative conditioning regimens

Cumulative incidences (solid lines) with 95% confidence interval (dashed lines) of disappearances of anti-donor IgG and IgM isohemagglutinin titres among 98 recipients of major/bidirectionally ABO-mismatched grafts.

Fig. 5. Impact of pre-HCT titre levels on post-HCT titre disappearance among major ABO/Bidirectionally mismatched recipients given nonmyeloablative conditioning
Hazard ratios (●) and 95% CIs (—) for the hazard of post-HCT disappearance of IgG (left panel) and IgM (right panel) titres for increasing quartiles of pre-HCT IgG and IgM titre levels, respectively, as compared to the lowest quartile for each ($p < 0.001$ for both).

Fig. 6. Impact of ABO-compatibility on survival among nonmyeloablative HCT recipients
No statistically significant differences were observed among the three cohorts ($P = 0.17$).

Patient and HCT Characteristics

Table 1

	Conditioning regimens			
	Myeloablative (N = 1353)		Non-Myeloablative (N = 503)	
Age at HCT (years)				
Median (range)	42.0 (0.6 – 67.0)		56.2 (2.6 – 78.9)	
	N	%	N	%
Primary Diagnosis				
AL	625	46.2	163	32.4
CL	352	26.0	62	12.3
Lymphoma	59	9.4	162	28.2
MDS	309	22.8	38	7.6
MM	8	0.6	98	19.5
Stem cell source				
PBSC	816	60.3	492	97.8
Marrow	533	39.4	11	2.2
ABO Groups				
Match	693	51.2	292	58.1
Minor	299	22.1	102	20.3
Major	268	19.8	89	17.7
}				
mismatch				
Bi-directional	93	6.9	20	4.0
Donor Type				
Related	716	52.9	265	52.7
Unrelated	637	47.1	238	47.3
Conditioning Regimen				
BU/CY	621	45.9	0	0
CY/TBI	589	43.5	0	0
FLU/TBI, 2Gy	0	0	398	79.1

	Conditioning regimens			
	Myeloablative (N = 1353)	Non-Myeloablative (N = 503)		
TBI 2Gy Only	0	0	101	20.1
Other [*]	143	10.6	4	0.8
GVHD Prophylaxis				
MTX/CSP or FK506	1155	85.4	0	0
MMF/CSP or FK506	84	6.2	485	97.4
Others [†]	114	8.4	18	2.6

Abbreviations: HCT= haematopoietic cell transplantation; AL= acute leukaemia; CL= chronic leukaemia; MDS= myelodysplasia; MM= multiple myeloma; CY=cyclophosphamide; BU=busulfan; FLU=fludarabine; TBI=total body irradiation; MTX=methotrexate; CSP=cyclosporine; MMF=mycophenolate mofetil; FK506=tacrolimus; GVHD=graft-versus-host disease.

^{*} Including regimens with antithymocyte globulin or FLU, or 300 cGy TBI in the case of a nonmyeloablative regimen.

[†] Including CSP, steroids or FK506 used without MMF or MTX, or used rapamycin. In nonmyeloablative setting, it includes the use of rapamycin.

Table II

Percentages of patients requiring at least one platelet or RBC transfusion.

	No. of Patients	% Patients Requiring Transfusions		
		Platelets	p-value*	RBC
Nonmyeloablative	503	36	†	75
Myeloablative	1353	99	<0.0001	96
Nonmyeloablative (PBSC only)	492	35	†	74
Myeloablative (PBSC only)	816	99	<0.0001	97
Nonmyeloablative				
Related grafts	265	29	†	68
Unrelated grafts	238	45	<0.0001	82
Nonmyeloablative				
ABO-match	292	34	†	70
Minor ABO-mismatch	102	36	0.71	78
Major/bidirectional ABO-mismatch	109	42	0.14	83
Nonmyeloablative Major/bidirectional ABO-mismatch				
Related grafts	50	38	†	80
Unrelated grafts	59	46	0.41	86

* p-value from Chi-square test.

† Reference group for comparisons.

RBC, red blood cell; PBSC, peripheral blood stem cells

Table III
Impact of ABO-compatibility on HCT outcomes among nonmyeloablative recipients.

Cumulative Incidence										
GVHD										
ABO	Graft Failure/ Rejection		Acute Grade II-IV		Extensive Chronic (2-year)		2-year Relapse		3-year Non-relapse Mortality	
	%	p-value	%	p-value	%	p-value	%	p-value	%	p-value
Match	4.8		58		57		35		21.9	
Minor-mismatch	3.9		63		62		31		20.4	
Major/bidirectional- mismatch	5.0	0.93	63	0.72	56	0.57	39	0.36	21.9	0.79

* P-value from logrank test comparing three ABO-compatibility groups.