Bone Marrow Transplantation (2005) 35, 489–495

www.nature.com/bmt

Post-transplant events

Impact of ABO incompatibility on outcome after allogeneic peripheral blood stem cell transplantation

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Summary:

Few studies have addressed the incidence of graft-versus-host disease (GVHD) or survival after ABO-incompatible allogeneic peripheral blood stem cell transplantation (PBSCT). We analyzed the clinical outcome of ABO incompatibility after allogeneic PBSCT. A total of 89 consecutive adult patients with hematological diseases including 49 ABO-identical, 20 major, 15 minor, and five bidirectional ABO-incompatible transplants were enrolled from four medical centers in Korea. No significant difference in engraftment times, graft failure, or transfusion requirements between groups was noted. A clinical diagnosis of severe immune hemolysis or pure red cell aplasia was not made for any patient after transplantation. The incidence of acute or chronic GVHD did not statistically differ between groups. With a median follow-up duration of 13 months (range, 0.5–61 months), the 3-year overall survival estimates for the ABO-identical, major/bidirectional, and minor group were 44.6.0 $\pm$ 9.0, 43.1 $\pm$ 11.6, and 43.8 $\pm$ 13.5%, respectively ($P = 0.8652$), while the 3-year disease-free survival estimates were 33.8 $\pm$ 7.6, 39.9 $\pm$ 11.4, and 45.7 $\pm$ 13.1%, respectively ($P = 0.8546$). We observed that time to neutrophil, platelet, and red blood cell engraftment, transfusion requirements, incidence of acute or chronic GVHD, relapse, and survival were not influenced by ABO incompatibility after allogeneic PBSCT from HLA-matched sibling donors.

Bone Marrow Transplantation (2005) **35,** 489–495.
doi:10.1038/sj.bmt.1704816
Published online 17 January 2005
Keywords: ABO; incompatibility; outcome; allogeneic; PBSCT

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Received 11 August 2004; accepted 27 October 2004
Published online 17 January 2005

Since the blood group system is inherited independently from the HLA system, approximately one-third of all stem cell transplants (SCT) are performed across the ABO blood group barrier. Minor ABO-incompatible SCT (eg O-type donor to A-type recipient) is characterized by the ability of the donor bone marrow to produce antirecipient isoagglutinins, major ABO-incompatible SCT (eg A-type donor to O-type recipient) by the presence of preformed antidonor isoagglutinins, and bidirectional incompatibility by a combination of both (eg A-type donor to B-type recipient). It has been believed that ABO incompatibility between donor and recipient is of minor importance for overall clinical outcome,[1–4] while increasing the risk of hemolytic reactions in all groups.[5] Recently, several studies reported that ABO incompatibility increased transplant-related mortality and represented a risk factor in allogeneic SCT.[6–8] Moreover, there are several lines of evidence that suggest minor ABO incompatibility may be associated with an increased risk of graft-versus-host disease (GVHD).[6,9]

Allogeneic peripheral blood stem cell transplantation (PBSCT) is increasingly being used instead of marrow because it allows more rapid hematologic recovery and has potent graft-versus-tumor effect in hematologic malignancies.[10,11] In contrast to marrow, delayed massive and fatal immune hemolysis due to rapid alloantibody production by donor-derived passenger B lymphocytes has been reported after allogeneic PBSCT if a minor or bidirectional ABO mismatch is present.[12,13] However, only a few studies have addressed the incidence of GVHD or survival after ABO-incompatible allogeneic PBSCT. Accordingly, we retrospectively analyzed the clinical outcomes of ABO incompatibility after allogeneic PBSCT with regard to time to engraftment, hemolysis, transplantation mortality, GVHD, and survival.

Patients and methods

Transplantation procedures

Retrospective analyses were performed on 89 consecutive adult patients with hematological diseases who received

allogeneic PBSCT between April 1998 and April 2003 at four medical centers in Korea. PBSCs were mobilized with a target of more than 3×10^6/kg of $CD34^+$ cells when using G-CSF alone, a G/GM-CSF concurrent combination, or sequential combination from matched donors, as previously reported.[14,15] The administration of G- and/or GM-CSF was continued and an apheresis repeated every morning until the target number of cells was obtained. The normal healthy donors were asked and agreed to undergo leukapheresis (10–20 l) on day 4 or 5. A standard 10-l leukapheresis was performed if the donor platelet count was $>70 \times 10^9$/l on successive days. Collected PBSCs were infused freshly without red blood cell (RBC) purging or removal of plasma even in cases of ABO mismatch. Detailed written and informed consent was obtained from all donors and patients before beginning the procedure.

Acute GVHD prophylaxis consisted of cyclosporin A (CyA) plus methotrexate ($n=57$), CyA alone ($n=20$), CyA plus mycophenolate mofetil ($n=11$), while infection prophylaxis consisted of ciprofloxacin (250 mg twice a day p.o.)/metronidazole (500 mg thrice a day p.o.)/fluconazole (400 mg once a day p.o.) beginning at initiation of conditioning and acyclovir (600 mg twice a day p.o.) from day −1. CMV antigenemia tests and chimerism studies using variable numbers of tandem repeats based on PCR with PB or BM mononuclear cells were conducted according to protocol guidelines.

Transfusion guidelines

Patients were transfused with RBCs to maintain hemoglobin concentrations greater than 8 g/dl, and with platelets to maintain a platelet count of greater than 20×10^9/l. All packed RBCs and platelets transfused were WBC-filtered and irradiated to 2500 cGy to reduce transfer of active leukocytes. The ABO type of blood components transfused after transplantation was defined by the blood groups of donors and recipients. Patients undergoing major or bidirectional ABO-incompatible transplants received RBCs of blood group O although group A or B recipients of cells from group AB donors could receive donor-type RBCs. This transfusion support was maintained until donor ABO type was demonstrable. Patients undergoing minor ABO-incompatible transplants were also transfused with group O RBCs although group AB recipients of cells from group A or B donors could receive donor-type RBCs. The preferred ABO type of platelet was that of the donor for major ABO-incompatible transplants and of the recipient for minor ABO-incompatible transplants. Bidirectional ABO-incompatible recipients received plasma-depleted platelet components of donor ABO type.

Laboratory testing

Routine laboratory tests after transplantation included daily complete blood counts (CBC). A chemistry profile including bilirubin was obtained three times per week or more frequently as needed for patient management. Lactate dehydrogenase (LDH) was measured weekly. Isoagglutinin titers for patients receiving major or bidirectional ABO-incompatible transplantation were examined pre-transplant and after transplantation until the titers were undetectable for 2 consecutive weeks or until discharge. Titers were classified by ABO-antigen (anti-A, anti-B) and antibody (IgM, IgG) types. A close observation of hemoglobin, bilirubin, and LDH was conducted to detect immune hemolysis in ABO-incompatible recipients earlier.

Definitions

The day of the stem cell infusion was defined as day 0. Myeloid engraftment was defined as the number of days taken to achieve an absolute neutrophil count (ANC) $\geqslant 0.5 \times 10^9$/l for 3 consecutive days. Platelet engraftment was defined as the time taken to achieve platelets $\geqslant 20 \times 10^9$/l without requiring a transfusion. RBC engraftment was defined as the day of appearance of 1% reticulocytes in the peripheral blood. Acute and chronic GVHD were diagnosed and graded according to the proposed criteria.[16,17]

Overall survival (OS) was defined as the time from transplantation until death from any cause. Disease-free survival (DFS) was defined as the time from transplantation until relapse or death, from whatever cause. Nonrelapse mortality (NRM) was defined as a death not related to recurrence or disease progression, such as an exacerbation of GVHD, opportunistic infections, ARDS, bleeding, graft failure, hepatitis, veno-occlussive disease, or thrombotic thrombocytopenic purpura. The OS and NRM rates beyond day 100 post transplant were also estimated to evaluate long-term effects of transplantation. High-risk diseases were defined as any disease relapsing after allogeneic or autologous SCT, acute leukemia more than the first CR, Ph+ acute lymphoblastic leukemia (ALL), advanced phase chronic myelogenous leukemia (CML), or primary refractory or multiple relapsed malignancies.

Statistical analysis

Clinical characteristics and outcomes of the groups according to ABO compatibility were compared using Fisher's exact test or Mann–Whitney's *U*-test. Kaplan and Meier's method was used to produce curves estimating DFS, OS, and NRM, while a log rank test was used to compare four groups. To adjust for potentially confusing variables, multivariate survival analysis using Cox's proportional hazard model was performed. The following variables were included in this analysis: age ($\geqslant$ *vs* <50 years), performance status (ECOG<2 *vs* $\geqslant 2$), diagnosis (CML *vs* others), disease status (standard- *vs* high-risk), conditioning (myeloablative *vs* nonmyeloablative), $CD34^+$ cell dose ($\geqslant$ *vs* $<6 \times 10^6$/kg), acute GVHD (grades 0, I *vs* grades II–IV) and chronic GVHD (yes *vs* no). All reported *P*-values are two-sided, and $P<0.05$ was assumed to be statistically significant. The statistical data were obtained using an SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

Results

Patient characteristics

Patient characteristics of the 49 ABO-identical, 20 major/five bidirectional, and 15 minor ABO-incompatible transplants are listed in Table 1. Overall, there was no significant difference in characteristics between groups. Disease entities included acute myeloid leukemia ($n=31$), chronic myeloid leukemia ($n=10$), ALL ($n=5$), aplastic anemia ($n=12$), lymphoma ($n=12$), myeloma ($n=6$), myelodysplastic syndrome ($n=8$), and paroxysmal nocturnal hemoglobinuria ($n=5$). In all, 45 (50.6%) and 44 patients (49.4%) had standard- and high-risk disease, respectively. PBSCs were mobilized with 10 μg/kg/day G-CSF (Filgrastim) alone ($n=53$, 59.6%), GM-CSF (Sargramostim) alone ($n=8$, 9.0%) or with a concurrent regimen ($n=15$, 16.9%) of 5 μg/kg/day G-CSF and 5 μg/kg/day GM-CSF for 5 days, or with a sequential regimen ($n=13$, 14.6%) of GM-CSF alone 10 μg/kg/day for 2 days followed by G-CSF alone 10 μg/kg/day for 3 days, from HLA-matched sibling donors.

Conditioning regimens, used according to the underlying disease or patient status, were as follows: BuCy regimen ($n=34$, 38.2%); TBI-based regimen ($n=8$, 9.0%); fludarabine-based nonmyeloablative regimen ($n=44$, 49.4%; fludarabine/busulfan, $n=25$; fludarabine/cyclophosphamide, $n=11$; fludarabine/melphalan, $n=6$; fludarabine/idarubicin/ara-C, $n=2$); low-dose TBI based nonmyeloablative regimen ($n=3$, 3.4%). The median dose of $CD34^+$ and infused MNC was 5.83×10^6/kg (range, 0.11–30.0×10^6/kg) and 7.59×10^8/kg (range, 0.02–17.7×10^8/kg), respectively.

Engraftment, transfusion, and hemolysis

Engraftment outcomes according to ABO compatibility are depicted in Table 2 and Figure 1. Successful engraftment was achieved in 81 patients (92%). Five patients experienced transplant-related mortality before engraftment. Three patients experienced primary ($n=1$) or secondary engraftment failure ($n=2$). Overall, the median engraftment day for the ANC, platelets, and RBC was 14 days (range, 6–41 days), 14 days (range, 0–56 days), and 14 days (range, 7–39), respectively. A median of 4 (range, 0–12) units of packed RBC and 20 (range, 0–66) units of platelet concentrates were transfused within the first 30 days after SCT, respectively. No significant difference in engraftment times, graft failure, or transfusion requirements between the three groups was noted. A clinical diagnosis of severe immune hemolysis or pure red cell aplasia (PRCA) resulting from the infusion of an ABO-incompatible graft and requiring specific medical intervention was not made for any patient after transplantation.

GVHD

Of 80 evaluable patients, 47 patients (58.8%) experienced acute GVHD, while 38 (47.5%) patients developed moderate to severe (grades II–IV) acute GVHD. Out of

Table 1 Characteristics of patients

Characteristics	*Total (n=89)*	*Identical (n=49)*	*Incompatible*			*P-value*
			Overall (n=40)	*Major/bidirectional (n=25)*	*Minor (n=15)*	
Median age, years (range)	37 (15–64)	36 (15–64)	39 (15–57)	35 (15–57)	41 (23–57)	NS
Gender						NS
Male	56 (62.9)	33 (67.3)	23 (57.5)	15 (60.0)	8 (53.3)	
Female	33 (37.1)	16 (32.7)	17 (42.5)	10 (40.0)	7 (46.7)	
Diagnosis						NS
AML	31 (34.8)	18 (36.7)	13 (32.5)	10 (40.0)	3 (20.0)	
CML	10 (11.2)	6 (12.2)	4 (10.0)	1 (4.0)	3 (20.0)	
ALL	5 (5.6)	1 (2.0)	4 (10.0)	3 (12.0)	1 (6.7)	
AA	12 (13.5)	7 (14.3)	5 (12.5)	4 (16.0)	1 (6.7)	
Others[a]	31 (34.8)	17 (34.7)	14 (35.0)	7 (28.0)	7 (46.7)	
Risk group						NS
Standard	45 (50.6)	27 (55.1)	18 (45.0)	13 (52.0)	5 (33.3)	
High	44 (49.4)	22 (44.9)	22 (55.0)	12 (48.0)	10 (66.7)	
Conditioning regimen						NS
Conventional	42 (47.2)	24 (49.0)	18 (45.0)	10 (40.0)	8 (53.3)	
Nonmyeloablative	47 (52.8)	25 (51.0)	22 (55.0)	15 (60.0)	7 (46.7)	
GVHD prophylaxis						NS
Cyclosporine A/MTX	57 (64.8)	32 (66.7)	25 (62.5)	16 (64.0)	9 (60.0)	
Cyclosporine A	20 (22.7)	12 (25.0)	8 (20.0)	4 (16.0)	4 (26.7)	
Cyclosporine A/MMF	11 (12.5)	4 (8.3)	7 (17.5)	5 (20.0)	2 (13.3)	

[a]Others included myelodysplastic syndrome, lymphoma, and paroxysmal nocturnal hemoglobulinemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; AA = aplastic anemia; MTX = methotrexate; MMF = mycophenolate mofetil; NS = not significant.

Table 2 Transplantation outcomes according to ABO compatibility

Characteristics	*Total (n = 89)*	*Identical (n = 49)*	*Incompatible*			*P-value*
			Overall (n = 40)	*Major/bidirectional (n = 25)*	*Minor (n = 15)*	
Engraftment (days)						
ANC	14 (6–41)	15 (9–41)	14 (6–24)	14 (7–24)	12 (6–21)	NS
Platelet	14 (0–56)	15 (0–56)	14 (0–48)	13 (0–48)	14 (0–26)	NS
RBC	14 (7–39)	14 (9–39)	14 (7–22)	15 (10–21)	14 (7–22)	
Engraftment failure (%)	3 (3.4)	1 (2.0)	2 (5.0)	1 (4.0)	1 (6.6)	NS
Transfusion requirement (first day 30)						
RBC (unit)	4 (0–12)	3.5 (0–12)	4 (0–8)	4 (0–10)	4.5 (0–11)	NS
Platelet (unit)	20 (0–66)	20 (0–60)	19 (0–66)	18 (0–66)	20 (0–42)	NS
Infections (first 30 days)						
Bacteremia	10 (11.2)	4 (8.2)	6 (15.0)	4 (16.0)	2 (13.3)	NS
Viral (CMV, herpes simplex)	20 (22.5)	8 (16.4)	12 (30.0)	6 (24.0)	6 (40.0)	NS
Fungal	12 (13.5)	5 (10.2)	7 (17.5)	4 (16.0)	3 (20.0)	NS
Acute GVHD (%)	(*n* = 80)	(*n* = 44)	(*n* = 36)	(*n* = 22)	(*n* = 14)	
Overall	47 (58.8)	28 (63.6)	19 (52.8)	10 (45.5)	9 (64.3)	NS
Grades II–IV	38 (47.5)	22 (50.0)	16 (44.4)	7 (31.8)	9 (64.3)	NS
Chronic GVHD (%)	(*n* = 68)	(*n* = 37)	(*n* = 31)	(*n* = 20)	(*n* = 11)	
Overall	41 (60.3)	23 (62.2)	18 (58.1)	10 (50.0)	8 (72.7)	NS
Extensive	21 (30.8)	12 (32.4)	9 (29.0)	5 (25.0)	4 (36.4)	NS
Relapse (%)	34 (38.2)	21 (42.9)	13 (32.5)	10 (40.0)	3 (20.0)	NS
Death (%)	45 (50.6)	24 (49.0)	21 (52.5)	13 (52.0)	8 (53.3)	NS

the evaluated 68 patients, 41 (60.3%) developed chronic GVHD (20 limited, 21 extensive). The incidence of acute or chronic GVHD did not statistically differ between the three groups (Table 2).

Transplant-related mortality, relapse, and OS

Within the first 30 days after allogeneic PBSCT, bacteremias occurred in 10 (11.2%) patients, viral infections including cytomegalovirus in 20 (22.5%) patients, and fungal infections in 12 (13.5%) patients, although the incidence of infection was not statistically different between the three groups (Table 2). When last assessed, death had occurred in 45 patients (50.6%). Early deaths and NRMs within 100 days post transplant were estimated as 21.3 ± 4.0 and $12.9 \pm 3.4\%$, respectively. The causes of death included relapse or persistent diseases ($n = 25$) and NRM (GVHD-related death; six cases, infection; six cases, graft failure; three cases, bleeding; three cases, toxic hepatitis; one case). The NRM rates for the ABO-identical, major/bidirectional, and minor-incompatible group were statistically not different ($P = 0.7159$) (Figure 2a).

With a median follow-up of 13 months (range, 0.5–61 months), relapse had occurred in 34 patients (38.2%), while 45 patients remained in continuous complete remission. The 3-year probability of relapse was estimated as $48.6 \pm 6.5\%$ overall and no difference was noted between the three groups. ($P = 0.4272$).

Currently, 44 patients are alive with a median follow-up of 17 months (range, 2–61 months). Overall, the 3-year OS and DFS estimates are 43.6 ± 6.0 and $37.8 \pm 5.6\%$, respectively. As shown in Figure 2, the 3-year OS estimates for the ABO-identical, major/bidirectional, and minor-incompatible group are 44.6 ± 9.0, 43.1 ± 11.6, and $43.8 \pm 13.5\%$, respectively ($P = 0.8652$), while the 3-year DFS estimates are 33.8 ± 7.6, 39.9 ± 11.4, and $45.7 \pm 13.1\%$, respectively ($P = 0.8546$). In a multivariate analysis adjusted for potential confounders, ABO compatibility was not found to be a significant factor influencing OS and DFS.

Discussion

Although the source of stem cells for allogeneic transplantation has largely moved to PBSC, which contain high numbers of lymphocytes and erythrocyte precursors, few studies have addressed the issue of ABO compatibility in patients receiving PBSCT. In the current study, we observed that time to neutrophil, platelet, and RBC engraftment, incidence of acute or chronic GVHD, relapse, and survival were not influenced by ABO incompatibility after allogeneic PBSCT from an HLA-matched sibling donor. These results are compatible with those previously reported in the BMT setting.[18,19] However, Stussi *et al*[8] reported in their study of 562 patients that survival was impaired in patients receiving bidirectional ABO-incompatible SCT as compared to ABO-identical SCT. They suggested that the higher mortality after bidirectional ABO-incompatible SCT might, at least partially, be attributed to the combination of major and minor ABO incompatibility with additive or synergistic enhancement of single adverse effects. Benjamin *et al*[6] also reported that patients with AML or MDS receiving ABO-incompatible BMT had a significantly increased death rate from infection and multiorgan failure within 100 days of transplantation, when blood products were transfused without prior

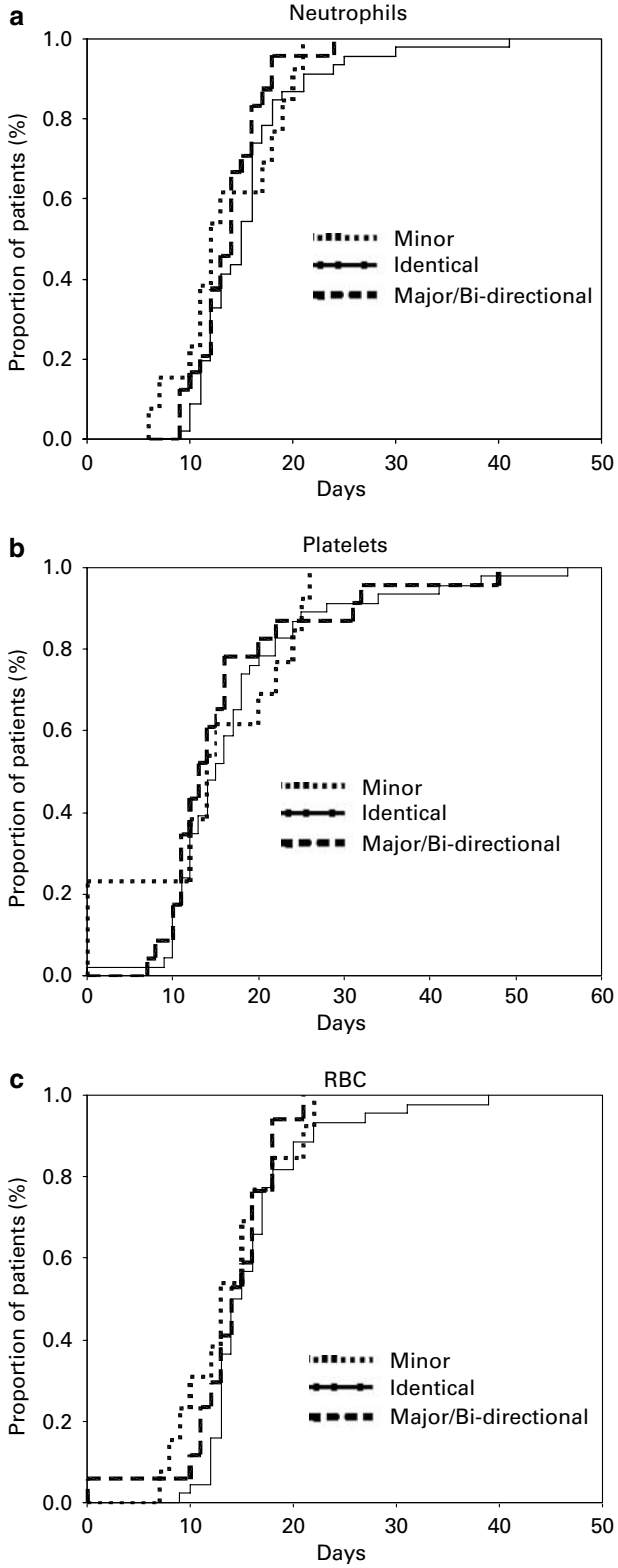

Figure 1 Engraftment of neutrophils (**a**), platelets (**b**), and RBC (**c**). There was no significant difference in the engraftment times between the three groups.

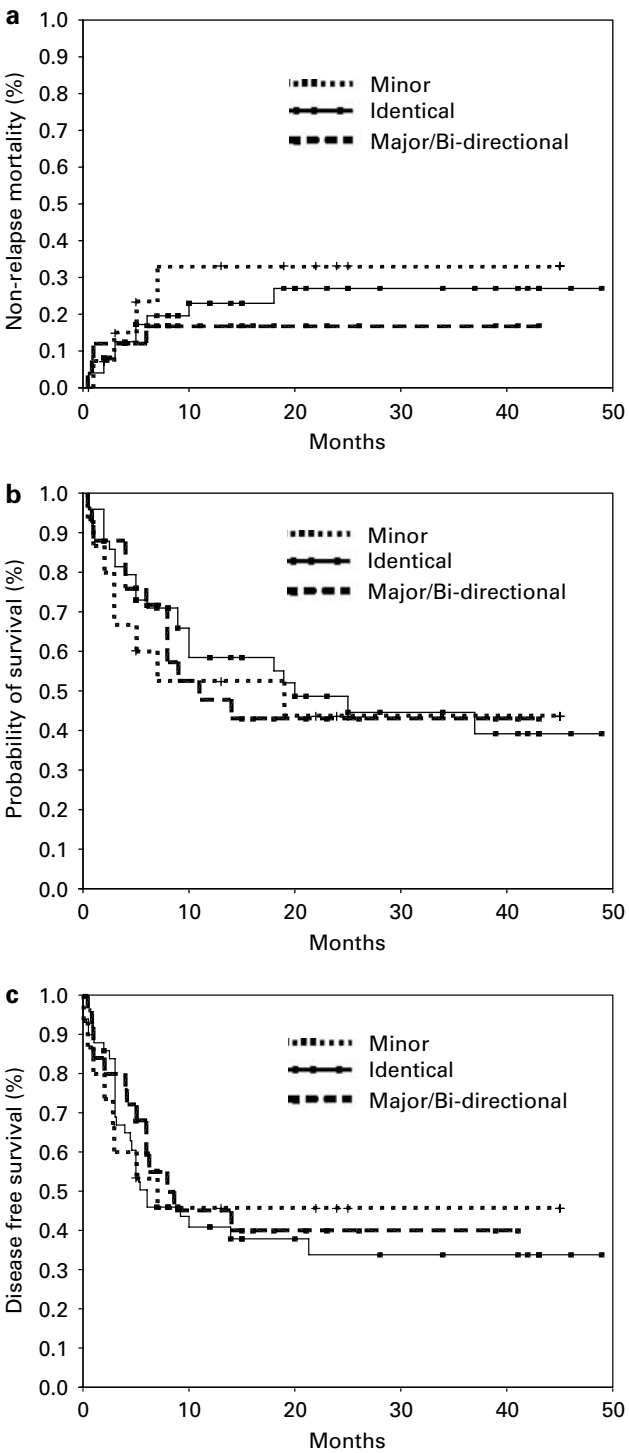

Figure 2 Comparison of non-relapse mortality (**a**), overall survival (**b**), and disease free survival (**c**) curves according to ABO compatibility. Overall, no statistical difference was observed between the three groups.

removal of donor plasma, resulting in the transfer of large amounts of antirecipient isoagglutinins. In contrast, these findings were not observed in the study[18] from the Seattle group, which was the largest focusing on ABO incompatibility, and since a clear biological explanation for this mechanism is currently not apparent, the impact of ABO incompatibility on survival after allogeneic SCT remains controversial.

Since A/B antigens are not only expressed on RBCs but have a wide tissue distribution, the antihost A/B antibodies produced after minor or bidirectional ABO-incompatible SCT may theoretically bind to and damage the host endothelium, which can potentially trigger GVHD.[20] In support of this hypothesis, it has been shown that patients receiving minor ABO-incompatible BMT had a higher risk of developing GVHD.[9] However, we found no significantly increased risk of developing acute or chronic GVHD in minor or bidirectional ABO-incompatible PBSCT in the present study, and other studies have also not demonstrated this difference. Given these results, it seems that ABO antigen and anti-A/B antibodies may have minor roles in the pathogenesis of GVHD, although this remains to be formally addressed.

Massive immune hemolysis or PRCA is one of the severe adverse effects of ABO-incompatible SCT, although this was not observed in the current study. Since PBSC grafts contain appoximately one log more $CD19^+$ B lymphocytes compared with marrow, delayed massive immune hemolysis due to donor-derived alloantibodies after minor or bidirectional ABO-incompatible allogeneic PBSCT has recently been reported.[12,13,21,22] Moreover, Worel *et al*[23] reported that severe immune hemolysis after minor ABO-incompatible allogeneic PBSCT occurred more frequently after nonmyeloablative than after myeloablative conditioning. They suggested that the use of other immunosuppressive agents than methotrexate (MTX) as GVHD prophylaxis, which inhibits proliferation of T- and B-lymphocytes and antibody production, might induce more common immune hemolysis after nonmyeloablative PBSCT. Even though 47 (52.8%) patients received nonmyeloablative conditioning in the present study, massive immune hemolysis was not observed. This might be due to the fact that CyA and MTX were administrated as GVHD prophylaxis in most (83.0%) cases.

PBSCs were mobilized with a GM-CSF and G-CSF combination regimen in 28 (31.5%) patients, which was associated with yields of $CD34^+$ cells equal to those seen with G-CSF alone, and with greater yields of primitive $CD34^+$ cells ($CD34^+/CD38^-/HLA\text{-}DR^+$ subset) as previously reported.[14,24] However, there was no difference in outcomes of ABO incompatibility between GM-CSF and G-CSF combination group and G-CSF alone group (data not shown).

In conclusion, the current study suggests that ABO incompatibility does not seem to affect treatment-related mortality, incidence of GVHD, or survival in allogeneic PBSCT from HLA-matched sibling donors. However, further analyses including larger patient numbers are warranted to clarify the impact of ABO incompatibility on the clinical outcome in allogeneic PBSCT settings.

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