Phase II study of non-myeloablative allogeneic bone marrow transplantation for B-cell lymphoma with post-transplantation rituximab and donor selection based first on non-HLA factors

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Abstract

Outcomes of non-myeloablative (NMA), HLA-haploidentical (haplo) related-donor allogeneic blood or marrow transplantation (allo BMT) with high-dose posttransplantation cyclophosphamide (PTCy) appear to be similar to those using HLA-matched donors. Thus, it may be possible to prioritize donor factors other than HLA-matching that could enhance antitumor activity. The Fc receptor polymorphism *FCGR3A*-158VV may confer greater sensitivity to rituximab than *FCGR3A*-158FF. In a prospective, phase II study of NMA, related-donor allo BMT with PTCy and posttransplantation rituximab for patients with B-cell lymphomas, we hypothesized that donor selection that prioritized *FCGR3A-158* polymorphism over HLA-matching would be feasible, safe and might improve outcomes. The primary endpoint was 1-year progression-free survival (PFS). Of 83 patients transplanted (median age 59 years), 69 (83%) received haplo grafts. Fifty-four (65%) received a graft that maintained or improved their Fc receptor polymorphism status. With 2.6-year median follow-up, the 1-year PFS and overall survival (OS) probabilities were 71% and 86%, respectively, with 1-year relapse and non-relapse mortality (NRM) probabilities of 20% and 8%. At 1-year, the probability of acute grades 2–4 graft-versus-host disease (GVHD) was 41%, with grade 3–4 acute GVHD probability of 5% and chronic GVHD probability of 11%. Among haplo transplants, the 1-year probabilities of PFS, OS, relapse, and NRM were 70%, 83%, 20%, and 10%, respectively. No differences in outcomes were observed based on donor *FCGR3A-158* polymorphism. Excess infection risk was not apparent with posttransplantation rituximab. Although donor selection based on *FCGR3A-158* polymorphism was not shown to influence PFS, this study suggests that donor selection based on criteria other than best HLA-match is feasible and safe. This study opens the way for the future investigation of donor prioritization based on

promising non-HLA factors that may improve anti-tumor activity and decrease relapse after allo BMT. This study was registered at www.clinicaltrials.gov as NCT00946023.

Introduction

Relapse after allogeneic blood or bone marrow transplantation (allo BMT) remains a major challenge and strategies are needed that can enhance anti-tumor alloimmunity without excess toxicity. Non-HLA factors such as donor killer-cell immunoglobulin-like receptor genotype have been shown to influence relapse rates and survival outcomes after unrelated donor BMT for acute leukemia.[1] However, such an approach ideally requires the availability of several potential donors to make selection feasible, as well as clinical equipoise in prioritizing non-HLA donor factors over the degree of HLA matching. High-dose, posttransplantation cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis for HLA-haploidentical (haplo), T-cell replete allo BMT is associated with acceptable rates of acute GVHD (aGVHD), non-relapse mortality (NRM), and graft failure as well as low rates of chronic GVHD (cGVHD), yielding results that appear comparable to other alternative donor sources and even HLA-matched related donors.[2–11] Allo BMT using PTCy thus provides a platform upon which to investigate outcomes when donors are selected based on factors other than best HLA-match.

FCGR3A is a low-affinity immunoglobulin gamma Fc receptor involved in natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity and is mainly expressed on NK cells. As compared to the *FCGR3A*-158FF (FF) polymorphism, *FCGR3A*-158VV (VV) and to a lesser extent *FCGR3A*-158VF (VF) have been associated with greater affinity to monoclonal antibodies and more favorable clinical responses to rituximab.[12–18] We hypothesized that the efficacy of posttransplantation rituximab in patients with B-cell lymphoma might be enhanced if donors were selected based on the affinity of their *FCGR3A-158* polymorphism for rituximab, as a means of enhancing a graft-versus-lymphoma effect.

In this phase II prospective clinical trial of NMA, related donor allo BMT using PTCy for patients with relapsed/refractory B-cell lymphoma, we integrated posttransplantation rituximab and evaluated a donor selection strategy prioritizing *FCGR3A-158* polymorphisms over degree of HLA matching. It was hypothesized that non-HLA graft characteristics which might enhance antitumor activity can be feasibly and safely prioritized over HLA matching and that donor selection based on *FCGR3A-158* polymorphisms coupled with posttransplantation rituximab could improve progression-free survival (PFS). Herein, we report the results of what is, to our knowledge, the first allo BMT study where donors were first prioritized using a factor other than HLA-matching.

Materials and Methods

Study Design

This was a single-center, prospective phase II clinical trial approved by the Johns Hopkins Institutional Review Board and conducted at the Sidney Kimmel Comprehensive Cancer

Center of Johns Hopkins Hospital (clinicaltrials.gov #NCT00946023). Patients were enrolled between August 2009 and April 2013. The primary objective was to determine the 1-year PFS, for the cohort and by donor FCGR3A-159 polymorphism, of patients with B-cell lymphoma following NMA, related-donor allo BMT using PTCy, integrated with posttransplantation rituximab and the prioritization of donors having a favorable *FCGR3A-158* polymorphism. Pre-defined secondary endpoints included the feasibility of identifying and selecting donors with the more favorable VV or VF *FCGR3A-158* polymorphism, estimates of overall survival (OS) and longer-term PFS, and estimates of the cumulative incidences of relapse, non-relapse mortality (NRM), aGVHD, and cGVHD. All patients gave written informed consent both for donor selection based on *FCGR3A-158* polymorphism status and for allo BMT. Outcomes of all 83 patients transplanted on this clinical trial are presented.

Patients

Eligibility for allo BMT included age ≤ 75 years old with a diagnosis of a CD20(+) B-cell lymphoma with at least one related donor who was at a minimum HLA-haploidentical at the HLA-A, -B, -C, -DR, and -DQ alleles. For low-grade B-cell lymphomas or chronic lymphocytic lymphoma/small lymphocytic leukemia (CLL/SLL), patients had to have failed at least two prior therapies excluding single agent rituximab, progressed through multi-agent chemotherapy, or undergone histologic transformation, unless the CLL/SLL harbored an 11q or 17p deletion. For aggressive B-cell non-Hodgkin lymphoma (NHL) or mantle cell lymphoma, patients had to have failed at least one prior multi-agent chemotherapy regimen. Patients were considered for allo BMT after either failing a prior autologous stem cell transplant or exhibiting disease features that made cure with autologous transplant seem unlikely, such as history of chemotherapy refractoriness, short remission after prior chemotherapy, or histologic transformation. For aggressive lymphomas, partial or complete remission (PR or CR) was required prior to allo BMT. Patients with active central nervous system involvement, HIV infection, or uncontrolled infection were excluded. End-organ function requirements included left ventricular ejection fraction of ≥ 35%, bilirubin ≤ 3.0 mg/dL, liver transaminases ≤ five times the upper limit of normal, and FEV1 and FVC ≥ 40% of predicted.

Donor selection algorithm

Donors were first-degree relatives or half-related siblings who were at least HLA-haploidentical, defined as having a shared HLA-haplotype between donor and patient at HLA-A, -B, -C, -DR, and –DQ based on allele or allele-group level typing. Relatives with no known contraindication to donation underwent *FCGR3A-158* polymorphism testing. Suitable donors were then prioritized as follows: 1) medically fit to donate, 2) absence of anti-donor HLA antibodies, 3) VV polymorphism, 4) VF polymorphism, 5) lack of major ABO incompatibility, 6) matched cytomegalovirus (CMV) IgG serostatus, 7) lack of minor ABO incompatibility, and 8) male donor preferred for male patients. In cases of more than one potential VV donor (or VF donor, in the absence of VV donors), HLA-matched donors were first prioritized over haplo donors and then donor age ≥ 18 was prioritized over donor age < 18, with donors ≤ 70 preferred.

FCGR3A-158 genotyping

The methods used for genotyping the *FCGR3A-158* polymorphism of patients and potential donors are provided as supplementary material (Supplementary Methods S1).

Transplantation regimen

NMA conditioning consisted of fludarabine, cyclophosphamide, and 200 cGy total body irradiation as previously described.[5] All grafts were T-cell replete and bone marrow-derived, with a target of 4×10^8 total nucleated cells per kilogram (kg) of recipient ideal body weight. GVHD prophylaxis in all cases consisted of high-dose PTCy (50 milligrams (mg)/kg/day intravenously (IV) on days +3 and +4), mycophenolate mofetil on days +5 through +35, and tacrolimus starting day +5. In the absence of GVHD or graft failure, tacrolimus was continued through day +180 with goal trough of 5 to 15 nanograms/milliliter, then discontinued without taper.

Supportive care measures were administered according to institutional standards. Granulocyte-colony stimulating factors (G-CSF) were given starting day +5 until the absolute neutrophil count (ANC) was 1000/microliter for three days. Prophylactic IV immunoglobulin G was permitted for hypogammaglobulinemia.

Rituximab 375 mg/m^2 IV was scheduled once weekly for eight weeks starting on day +30 +/− 3 days, contingent on neutrophil recovery. The start of rituximab was otherwise delayed. The rituximab schedule could also be delayed or interrupted at physician discretion if there were concerns about its safety, including severe unexplained cytopenias, active significant infection, or significant GVHD. Rituximab was administered early after allo BMT, as this is the period of highest relapse risk.

Definition of endpoints

Disease status was defined per standardized response criteria.[19,20] Patients with stable or progressive disease by the referenced criteria were categorized as having "active disease" at the time of allo BMT. Acute GVHD was graded per Keystone criteria.[21] Chronic GVHD was evaluated using the National Institutes of Health Working consensus criteria and Seattle criteria.[22,23] The hematopoietic cell transplantation-specific comorbidity index (HCT-CI),[24] comorbidity-age index,[25] and the refined disease risk index (DRI)[26] were retrospectively determined.

Neutrophil recovery was the first of three consecutive days with an ANC 500/mm^3. Platelet recovery was the first day with a platelet count of 20,000/mm^3 without platelet transfusion in the preceding week. Death before count recovery was considered a competing risk for count recovery. Full donor chimerism was defined as 95% donor cells in the blood or bone marrow. Primary graft failure was defined as < 5% donor chimerism by ~ day +60 in unsorted cells and/or CD3 cells, without detectable bone marrow malignancy. Secondary graft failure was defined as < 5% donor chimerism after the initial presence of donor cells. Late-onset neutropenia (LON) was defined as an ANC of 1000/mm^3 (Grade 3) or 500/mm^3 (Grade 4) starting four weeks after last rituximab therapy through 12 months after

the last rituximab dose, or until relapse.[27,28] Attribution of LON to rituximab is further described in the results section.

All time-to-event endpoints were measured from the date of allo BMT. PFS was the time to disease relapse, progression, unplanned treatment of persistent disease, or death from any cause. OS was the time to death from any cause. Competing risks for aGVHD and cGVHD included any PFS failure or < 5% donor chimerism from any cause. Relapse/progression and NRM were considered competing risks. Patients without events were censored at the date of their last evaluation.

Statistical analysis

Differences in group characteristics were compared using the Fisher's exact test for categorical variables and the Kruskall-Wallis test for continuous variables. PFS, DFS, and OS were estimated using the Kaplan-Meier method with 95% confidence intervals (CIs) and compared between groups using the log-rank statistic.[29] Cumulative incidences of relapse, NRM, GVHD, and count recovery were estimated by competing risk analysis using Fine and Gray's method.[30,31] Two-sided p-values < 0.05 were considered significant. Data were analyzed using the R program, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://R-project.org/). The dataset was locked for analysis on October 27, 2014.

Results

Patient characteristics

Eighty-three consecutive patients with B-cell lymphoma, median age 59 years (range, 34–75), were transplanted on this trial. Patient and transplant characteristics overall and according to donor *FCGR3A-158* polymorphism are summarized in Table 1. Sixty-nine patients (83%) received haplo grafts, and 13 (17%) patients received grafts from HLA-matched related donors, with no difference by *FCGR3A-158* donor polymorphism in the proportion receiving haplo grafts. Diagnoses included aggressive, *de novo* or transformed NHL (59%), mantle cell lymphoma (17%) and low-grade B-cell malignancies (23%). Recipients of haplo allo BMT (n=69) had patient and transplantation characteristics that were similar to the cohort as a whole, Supplementary Table S2. The majority of patients (60%) had intermediate-risk disease by the refined DRI, which was similarly distributed across the donor *FCGR3A-158* polymorphism groups. More patients with a high age-comorbidity index received FF grafts (p=0.03).

Donor selection

The distribution of the *FCGR3A-158* polymorphism among patients was 11 (13%) VV, 43 (52%) VF, and 29 (35%) FF. Of 270 donors tested for these polymorphisms (median 3 donors tested per patient, range 1–7), 35 (13%) had the VV polymorphism, 121 (45%) were VF, 111 (41%) were FF, and 3 (1%) had unverified polymorphism results. From this, 54 patients (65%) were able to receive a VF or VV graft, of which 29 (54%) received a graft with a more favorable *FCGR3A-158* polymorphism and 25 (46%) received a graft with the same favorable VV (n=5) or VF (n=20) polymorphism. In five cases (6%), a haplo donor

was selected over a matched donor in order to use a more favorable polymorphism. In 12 cases (14%), the person with the most favorable polymorphism was unsuitable to donate, resulting in five cases (6%) where a donor with a less favorable polymorphism than the recipient was used.

Engraftment and Chimerism

The estimated cumulative incidence of neutrophil recovery was 98% (95% confidence interval (CI) 94–101%) by day +30 (median, 16 days). The cumulative incidence of platelet recovery was 98% (95% CI 94–101%) by day +60 (median, 24 days). Of 81 evaluable patients, primary graft failure occurred in two patients (2.5%), with autologous recovery of hematopoiesis in both cases. Unsorted chimerism at day +60 was 95% donor or greater for 70 patients; an additional 10 patients had mixed chimerism (5–94% donor cells) and one patient had 0% donor cells. CD3 chimerism at day +60 was 95% donor or greater for 69 patients, mixed for nine patients, 0% for two patients, and not evaluated in one patient who was 100% donor in unsorted blood. One patient with mixed chimerism on day +60 developed secondary graft failure on day +112, with autologous hematopoietic recovery and ongoing disease-free survival.

Toxicity

By competing risk analysis, the estimated probability of NRM for the cohort was 5% (95% CI 0–9%) at day +180 and 8% (95% CI 2–14%) at one year, Figure 1A. Causes of NRM (n=12) were non-neutropenic infection (n=5, with three in the setting of GVHD treatment), neutropenic infection (n=3), treatment-related myeloid neoplasm (n=2), pulmonary embolism (n=1), and decompensated alcoholic cirrhosis (n=1). At one year, the estimated probability of grade 2–4 aGVHD was 41% (95% CI 30–52%), although most cases were grade 2 with an estimated probability of grade 3–4 aGVHD at 1-year of 5% (95% CI 0–9%), Figure 1B. The estimated probability of any cGVHD was 11% (95% CI 4–18%) at one year and 14% (95% CI 6–21%) at two years. The probability of systemic therapy for cGHVD was 9% (95% CI 2–15%) at one year and 10% (95% CI 3–17%) at two years, Figure 1C.

Sixty-seven patients (81%) received all eight planned doses of posttransplantation rituximab. Reasons for fewer doses of rituximab are outlined in the footnote of Table 1. Grade 3–4 LON was documented in 38 of the 82 (46%) patients who received posttransplantation rituximab, 25 (68%) of whom had minimal or no associated clinical findings; 23 were completely asymptomatic, one had oral ulcers requiring no therapy, and one required oral antibiotics for sinusitis. At the time of LON diagnosis, 22 of 38 patients were assessed for donor chimerism, of which 19 had 100% donor cells, two had mixed chimerism (81% and 95% donor cells in unsorted peripheral blood), and one had secondary graft failure. An additional 11 patients were not assessed for chimerism at the time of LON, but were assessed in the two months preceding or following LON; of these, ten had full donor chimerism on all assessments while one had 93%/81% donor cells in the unsorted peripheral blood in the two months preceding/following LON. By *FCGR3A-158* polymorphism, there was no difference detected in the percentage of patients with known grade 4 LON (p=0.79); the rates of hospitalization for serious grade 4 LON-associated infections and fatal infections were also similar between groups. Thirteen patients (16%) were hospitalized for grade 4

LON. Of those hospitalized, six patients had LON that was likely not attributable to rituximab; five patients had neutropenia in the setting of multilineage cytopenias during treatment for CMV (n=4) and/or GVHD (n=3), one of which was further complicated by fatal adenovirus encephalitis, and one patient had pancytopenia in the setting of toxoplasmosis infection. There were seven patients hospitalized with LON-associated infections potentially attributable to rituximab including three fatal infections (one Pseudomonas pneumonia, one presumed nocardiosis, and one presumed histoplasmosis).

Survival outcomes and relapse

The median follow-up was 2.6 years for all patients by the reverse Kaplan-Meier method and 2.4 years (range 1.0 to 5.0 years) among surviving patients. PFS, OS, and relapse point estimates with 95% CIs are shown in Table 2. In the group overall, the estimated 1-year PFS and OS were 71% and 86%, with corresponding 2-year probabilities of 60% and 76%, Figure 1D. By competing risk analysis, the estimated 1-year cumulative incidence of relapse for the cohort was 20% at one year and 27% at two years, Figure 1A.

Outcomes by subgroups

Point estimates for relapse, PFS, and OS for subgroups are shown in Table 2. By donor *FCGR3A-158* polymorphism, the 1-year estimated cumulative incidence of relapse was 18% for VV, 23% for VF, and 17% for FF grafts, Figure 2A. The estimated 1-year PFS was 82%, 70%, and 65% for VV, VF, and FF grafts, respectively (Figure 2B, log-rank p=0.44), with corresponding estimated 1-year OS of 94%, 86%, and 78%, log-rank p=0.43. The estimated 1-year probability of NRM was 0% (95% CI 0–0%) for VV, 7% (95% CI 0–15%) for VF, and 17% (95% CI 1–33%) for FF.

Among those receiving haplo grafts (n=69), the 1-year estimated cumulative incidence of relapse was 20% (Figure 3A, with NRM; Table 2). The estimated 1-year PFS and OS were 70% and 83%, respectively, with corresponding 2-year probabilities of 63% and 73% (Figure 3B, Table 2). At one year, the probability of grade 2–4 aGVHD was 45% (95% CI 33–57%), grade 3–4 aGVHD was 6% (95% CI 0–11%), cGVHD was 13% (95% CI 5–21%), and NRM was 10% (95% CI 3–17%).

Discussion

Herein we report the outcomes of a phase II study of NMA, related-donor allo BMT for B-cell lymphomas incorporating PTCy, posttransplantation rituximab, and donor selection based on *FCGR3A-158* polymorphism. The PFS and OS were favorable for the cohort as a whole and appear improved as compared to the historical outcomes of patients with B-cell lymphomas who received NMA haplo allo BMT using PTCy without rituximab, where the estimated 1-year PFS is lower at around 50%, based on our published and unpublished data.[5] The survival outcomes presented here are also consistent with other recent reports using posttransplantation rituximab, suggesting that this approach may improve disease control after allo BMT.[32,33] Our study is unique given the use of haplo grafts in the majority of patients and the implementation of a donor selection process based on non-HLA factors.

In a recently published prospective phase II trial of NMA HLA-matched allo BMT for B-cell lymphoma with pre- and posttransplantation rituximab, the 2-year event-free survival and OS probabilities were similar to ours at 72% and 78%, respectively.[32] As these data were not available in planning the trial, we had not anticipated such good survival outcomes. The overall favorable outcomes virtually precluded finding significant differences based on *FCGR3A-158* polymorphism. The potential benefits of *FCGR3A-158*-guided donor selection might be further obscured if such benefits are associated only with particular subtypes of B-cell lymphoma or are associated with only particular regimens as has been suggested.[15,17,34]

LON was documented in nearly half of patients, as has been shown by others.[32] However, it can be difficult to attribute neutropenia to rituximab versus other etiologies (e.g. infection) in the allo BMT setting. Importantly, LON was asymptomatic in the majority of the patients, and the use of posttransplantation rituximab did not appear to translate into an increased risk of severe infection.

The favorable PFS and OS, as well as low relapse rates, suggest that posttransplantation rituximab may have a direct anti-tumor effect or modulate graft related anti-tumor immune effects. With regard to the latter, we note that the incidence of grades 2–4 aGVHD in the present study appears higher than has previously been reported for NMA haplo BMT with PTCy but no rituximab. However, this was attributable to higher rates of grade 2 aGVHD, with rates of grade 3–4 aGVHD that were not higher than previous reports.[5,6,8,10] As the principal difference between the platform in prior studies and the current study is the inclusion of posttransplantation rituximab here, this suggests that rituximab may impact aGVHD risk. While there is evidence to support the role of posttransplantation rituximab in preventing or treating cGVHD,[35–42] less is known about how rituximab might influence aGVHD risk.[43] The cellular interactions mediating acute and chronic GVHD are complicated and the relative roles of donor and host B cells, including lymphoma cells, in GVHD pathogenesis are incompletely understood. We hypothesize that rituximab-induced killing of lymphoma cells early after allo BMT promotes the immunogenic cross-presentation of lymphoma-derived minor histocompatibility and tumor antigens to non-tolerant donor T-cells, thereby augmenting both aGVHD and the graft-versus-lymphoma effect, respectively.[44] However, other interpretations of our data are certainly possible.

Of broader significance, this study demonstrates the feasibility and safety of selecting related donors based on factors other than degree of HLA matching. The haplo outcomes presented here are similar to those previously published for matched related or unrelated donor allo BMT.[2,7] The relatively low rates of grade 3–4 aGVHD, cGVHD requiring systemic therapy, graft failure, and NRM with haplo grafts suggests that HLA matching need no longer be a barrier to optimal donor selection. This study provides support for future trials that similarly aim to identify and select donors based on factors apart from HLA that are hypothesized to improve the antitumor activity of the graft and decrease relapse after allo BMT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Donor selection prioritizing non-HLA factors can be feasible and safe

- Rituximab after allo BMT is associated with favorable survival outcomes

- Donor *FCGR3A-158* polymorphism does not appear to influence outcomes after allo BMT
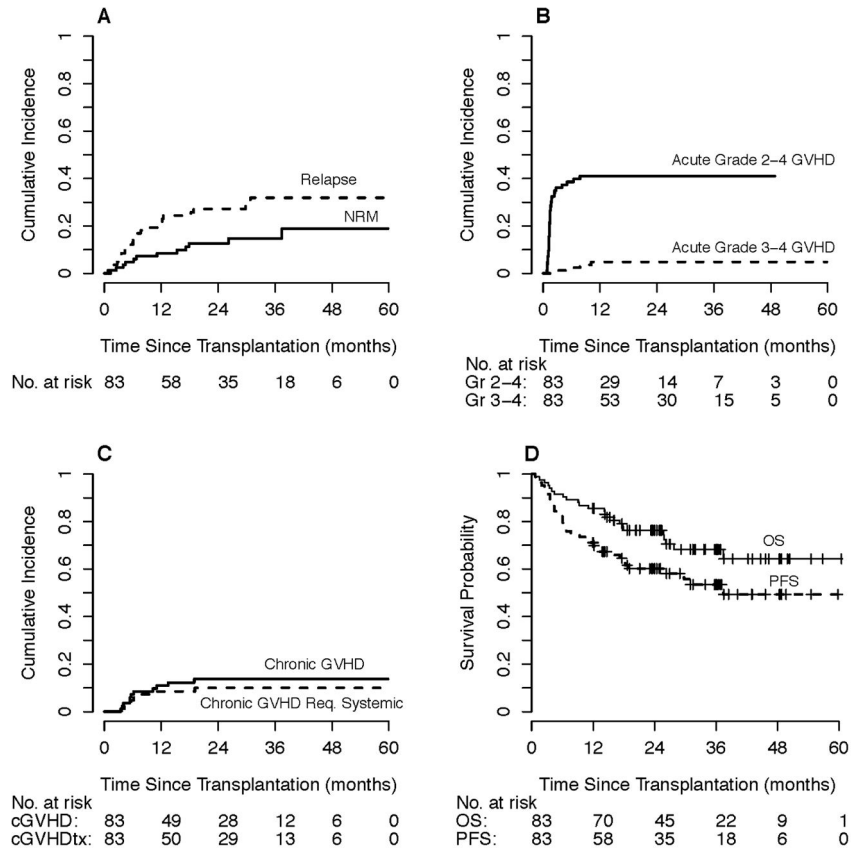
Figure 1. Overall outcomes of non-myeloablative, related-donor bone marrow transplantation with posttransplantation high-dose cyclophosphamide and rituximab (n=83)

A) Relapse and non-relapse mortality by competing risk analysis. B) Acute graft-versus-host disease (grades 2–4 and grades 3–4) by competing risk analysis. C) Chronic graft-versus-host disease (overall and requiring systemic therapy) by competing risk analysis. D) Progression-free and overall survival. Of these 83 patients, 69 received HLA-haploidentical grafts.

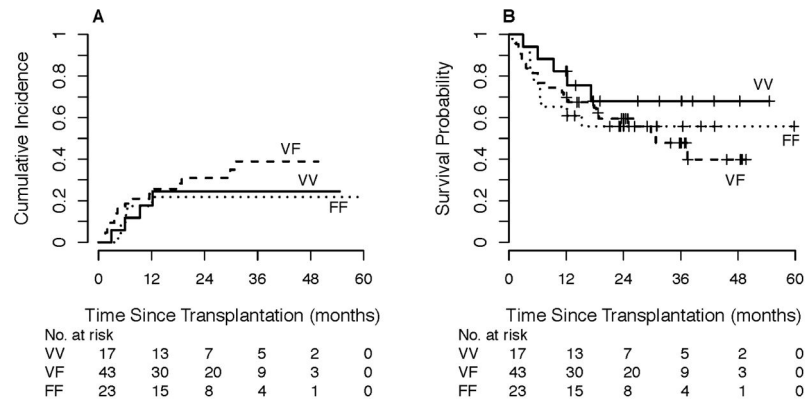**Figure 2. Outcomes of non-myeloablative, related-donor bone marrow transplantation according to donor *FCGR3A-158* polymorphism**

A) Relapse by competing-risk analysis. B) Progression-free survival.
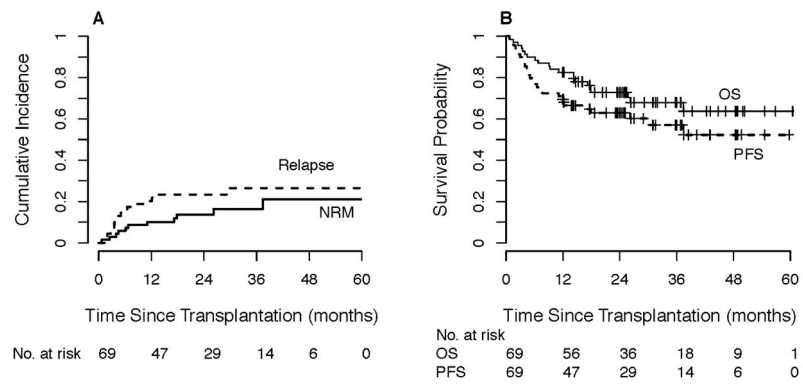
Figure 3. Outcomes of non-myeloablative, related HLA-haploidentical donor bone marrow transplantation (n=69)

A) Relapse and non-relapse mortality by competing risk analysis. B) Progression-free and overall survival.

Table 1

Patient and transplant characteristics overall and by donor *FCGR3A-158* polymorphism

	All patients (n=83)	VV donor (n=17)	VF donor (n=43)	FF donor (n=23)	p^a
Patient age at BMT					
Median, years (range)	59 (34–75)	55 (38–69)	59 (34–75)	59 (40–75)	0.82
Age ≥ 60, n (%)	39 (47%)	8 (47%)	20 (47%)	11 (49%)	0.99
Male sex, n (%)	56 (67%)	12 (71%)	24 (56%)	20 (87%)	0.03
Disease, n (%)					
Aggressive lymphoma[b]	49 (59%)	6 (35%)	31 (72%)	12 (52%)	
MCL	13 (17%)	5 (29%)	4 (9%)	4 (17%)	
CLL/SLL[c]	10 (12%)	2 (12%)	2 (5%)	6 (26%)	
FL, grade 1–2 or MZL[c]	9 (11%)	3 (18%)	5 (12%)	1 (4%)	
nLP HL	2 (2%)	1 (6%)	1 (2%)	0 (0%)	
Disease status at allo BMT, n (%)					0.54
Complete remission	43 (52%)	12 (71%)	20 (47%)	11 (48%)	
Partial remission	29 (35%)	4 (24%)	17 (40%)	8 (35%)	
Active disease	11 (13%)	1 (6%)	6 (14%)	4 (17%)	
Transformed lymphoma, n (%)[d]	22 (27%)	1 (6%)	14 (33%)	7 (30%)	0.10
Prior autografting, n (%)	12 (14%)	4 (24%)	5 (12%)	3 (13%)	0.46
Refined DRI, n (%)					0.10
Low risk	28 (34%)	10 (59%)	10 (23%)	8 (35%)	
Intermediate risk	50 (60%)	7 (41%)	30 (70%)	13 (57%)	
High/very high risk	5 (6%)	0 (0%)	3 (7%)	2 (9%)	
HCT-CI score, n (%)					0.12
0 (low risk)	17 (20%)	2 (12%)	12 (28%)	3 (13%)	
1–2 (intermediate risk)	41 (49%)	12 (71%)	20 (47%)	9 (39%)	
3 (high risk)	25 (30%)	3 (18%)	11 (26%)	11 (48%)	
Age-comorbidity index, n (%)					0.03
0–2 (low risk)	41 (49%)	10 (59%)	25 (58%)	6 (26%)	

	All patients (n=83)	VV donor (n=17)	VF donor (n=43)	FF donor (n=23)	p[a]
3 (high risk)	42 (51%)	7 (41%)	18 (42%)	17 (74%)	
HLA matching					0.93
HLA-haploidentical	69 (83%)	14 (82%)	35 (81%)	20 (87%)	
HLA-matched[e]	14 (17%)	3 (18%)	8 (19%)	3 (13%)	
Median donor age, years (range)	41 (13–72)	41 (16–64)	42 (13–72)	42 (20–65)	0.78
Female into male, n (%)	22 (27%)	3 (18%)	11 (26%)	8 (35%)	0.51
Patient CMV seropositive, n (%)	30 (36%)	10 (59%)	15 (35%)	5 (22%)	0.06
CMV matching, n (%)					0.30
Donor (−)/Recipient (−)	36 (43%)	4 (24%)	18 (42%)	14 (61%)	
Donor (+)/Recipient (−)	17 (20%)	3 (18%)	10 (23%)	4 (17%)	
Donor (−)/Recipient (+)	15 (18%)	5 (29%)	7 (16%)	3 (13%)	
Donor (+)/Recipient (+)	15 (18%)	5 (29%)	8 (19%)	2 (9%)	
Infused cell dose, median (range)					
TNC x 10^8/kg	4.5 (2.2–7.7)	4.5 (3.1–6.1)	4.3 (2.2–7.7)	4.6 (3.2–6.1)	
CD34$^+$ cells x 10^6/kg	4.5 (1.8–25.1)	4.1 (1.8–25.1)	4.7 (2.1–9.8)	4.4 (2.1–8.6)	
CD3$^+$ cells × 10^7/kg	4.1 (1.6–10.4)	5.1 (2.3–6.8)	3.7 (1.6–10.4)	4.1 (2.8–9.7)	
Doses of post-BMT rituximab, n (%)					0.92
8	67 (81%)	15 (88%)	34 (79%)	18 (78%)	
6–7[f]	8 (10%)	2 (12%)	4 (9%)	2 (9%)	
4–5[f]	4 (5%)	0 (0%)	3 (7%)	1 (4%)	
1–3[f]	3 (4%)	0 (0%)	2 (5%)	1 (4%)	
0[g]	1 (1%)	0 (0%)	0 (0%)	1 (4%)	

Abbreviations: VV, donor homozygous for the V *FCGR3A-158* allele; VF, donor with V and F *FCGR3A-158* alleles; FF, donor homozygous for the F *FCGR3A-158* allele; BMT, bone marrow transplantation; MCL, mantle cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; nLP HL, nodular lymphocyte predominant Hodgkin lymphoma; DRI, disease risk index; HCT-CI, hematopoietic cell transplant-comorbidity index; CMV, cytomegalovirus; TNC, total nucleated cells

[a]P values are for differences between the three FCGR3A polymorphism groups

[b]Diffuse large B-cell lymphoma (DLBCL) *de novo* (n=16) or transformed (n=21), T-cell/histiocyte rich large B-cell lymphoma (n=2), primary mediastinal large B-cell lymphoma (n=2), nLP HL, nodular... FL, grade 3 (n=8)

[c]Excluding transformed lymphoma

[d] Transformation was defined as evolution of a low-grade lymphoma into an aggressive lymphoma, including transformation of FL grade 1–2 into FL grade 3. Changes from FL grade 3 to DLBCL were not considered a transformation. Transformations included DLBCL out of low-grade lymphoma (n=21) and aggressive B-cell lymphoma not otherwise specified out of CLL (n=1)

[e] Including two patients who received grafts from genetically haplo donors who were phenotypically 10/10 HLA-matched

[f] Reasons that 1–7 doses of rituximab were given: unconfirmed (n=4), neutropenia (n=2), graft-versus-host disease (n=2), musculoskeletal pains (n=2), death prior to completion of rituximab (n=2), inadequate intravenous access (n=1), graft failure (n=1), relapse (n=1)

[g] Rituximab not given due to early death prior to neutrophil recovery (n=1)

Table 2

Point estimates for relapse, progression-free survival, and overall survival for the cohort and subgroups.

Group	N	Probability (%) with 95% confidence interval							
		Relapse		Progression-free survival		Overall survival			
		1 year	2 years	1 year	2 years	1 year	2 years		
All patients	83	20 (13–28)	27 (17–37)	71 (62–82)	60 (52–70)	86 (78–93)	76 (67–86)		
Aggressive NHL	49	22 (11–34)	25 (12–37)	69 (58–84)	62 (49–78)	86 (76–96)	74 (62–88)		
Haplo	69	20 (11–30)	23 (13–34)	70 (60–81)	63 (52–76)	83 (74–92)	73 (63–84)		
VV or VF donor	60	22 (11–32)	29 (17–41)	73 (63–85)	62 (50–76)	88 (81–97)	79 (69–90)		
VV donor	17	18 (0–36)	25 (3–46)	82 (66–100)	68 (48–96)	94 (84–100)	87 (71–100)		
VF donor	43	23 (10–36)	31 (17–45)	70 (56–85)	59 (46–76)	86 (76–97)	76 (64–90)		
FF donor	23	17 (1–33)	22 (4–39)	65 (44–88)	56 (39–81)	78 (63–97)	69 (52–91)		

There were no statistically significant differences in relapse, progression-free survival, or overall survival according to donor *FCGR3A-158* polymorphism. Disease-free survival was virtually identical to progression-free survival and is therefore not shown separately.

Abbreviations: NHL, non-Hodgkin lymphoma; VV, donor homozygous for the V *FCGR3A-158* allele; VF, donor with V and F *FCGR3A-158* alleles; FF, donor homozygous for the F *FCGR3A-158* allele