Rituximab-based allogeneic transplant for chronic lymphocytic leukemia with comparison to historical experience

Rituximab-based allogeneic Transplant for Chronic Lymphocytic Leukemia with Comparison to Historical Experience

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Abstract:

Background: Relapse of high-risk chronic lymphocytic leukemia (CLL) after allogeneic hematopoietic cell transplantation (HCT) has remained a clinical challenge. In this phase-II trial, we studied whether the addition of peri-transplant rituximab would harness graft-versus leukemia effects and reduce the relapse risk compared to the historical controls. Patients and Methods: Between 2009-2014, 55 patients received fludarabine and low-dose total body irradiation before HCT combined with rituximab on days -3, +10, +24, +36. For comparison, we analyzed data from 157 CLL patients who had an HCT between 1997 and 2014 without peri-transplant rituximab. Both cohorts (n=215) contributed to the multivariate analyses. Results: The 3-year estimates of overall survival (OS), progression-free survival (PFS), relapse and non-relapse mortality (NRM) in rituximab-treated and historical patients were (53% vs. 50%; p=0.8), (44% vs. 42%; p=0.63), (17% vs. 31%; p=0.04) and (38% vs. 28%; p =0.2), respectively. Patients with no comorbidities who received rituximab-conditioning had an OS rate of 100% and 75% at 1 and 3 years, respectively, with no reported NRM. In multivariate analysis, rituximab-treatment was associated with lower relapse rates both in the overall cohort [hazard ratio (HR): 0.34, *p*=0.006] and in patients with high-risk cytogenetics (HR: 0.21, p =0.0003) Conclusions: Peri-transplant rituximab reduced relapse rates regardless of high-risk cytogenetics. HCT is associated with minimal NRM in patients with no comorbidities and is a viable option for patients with high-risk CLL.

Clinical trial information: NCT00867529

Background

Allogeneic hematopoietic cell transplantation (HCT) remains the only potentially curative treatment for chronic lymphocytic leukemia (CLL) but is complicated by non-relapse mortality (NRM).(1) In recent years, novel agents like B-cell receptor inhibitors (ibrutinib and idelalisib) and a BCL-2 antagonist (venetoclax) have extended survivals for CLL patients in general and especially for those with high-risk features for whom conventional chemo-immunotherapy regimens are not effective.(2-4) As a result, a decreasing number of CLL patients is offered HCT nation-wide per the Center for International Blood and Marrow Transplant Research (CIBMTR).(5) Despite the promising results from the novel agents, their efficacy is limited in high-risk CLL patients and outcomes after progression while on these agents are dismal.(6-9) In addition, the current agents require indefinite duration of treatment that can increase the cost and carries the risk of poor drug adherence.(10, 11) Therefore, and while newer agents and combinations are being studied in this setting, exclusive use of novel agents as the only therapeutic strategy in high-risk CLL patients seems to be premature and incorporation of HCT in selected patients with a reasonable risk/benefit ratio is still part of the standard approach to high-risk CLL patients.(12-14) In the meantime, interventions to improve the efficacy of allogeneic HCT for CLL are required.

CLL predominantly affects the elderly. Patients are referred to allogeneic HCT only after they have become unresponsive to other therapies, which is usually many years after diagnosis. Given their age and frequent comorbidities, patients with CLL are generally conditioned for HCT with reduced intensity regimens in order to minimize associated toxicities. Therefore, eradication of CLL cells relies largely on graft-versus-leukemia (GVL) effects. While GVL effects begin immediately after HCT, they are initially attenuated both by the need of the donor immune system to establish itself and the broad immunosuppression from drugs given to control graft-versus-host disease (GVHD). Given the reliance on GVL effects and their initial impairment, relapse of CLL has been the most pressing problem after allogeneic HCT, especially in patients with bulky disease or bad risk cytogenetics. This has affected long-term outcomes after HCT. In order to reduce the relapse risk, we evaluated the use of peri-transplant rituximab in a phase II trial. The trial was based on the hypothesis that rituximab enhanced early direct cell kill through antibody-dependent cytotoxicity (15). Moreover, by inducing apoptosis, rituximab can promote uptake and cross-presentation of cell-derived peptides by antigen-presenting dendritic cells resulting in cross-priming and generation of donor-derived cytotoxic cells which might result in an earlier switch-on of GVL effects. (16-18). Here we compare the results of the phase II trial to historical patients not given rituximab. The initial report of the

historical experience is previously published and the outcomes were updated for the purpose of this analysis(15).

Patient and Methods

Between 2009 and 2014, 55 CLL patients were given HCT after conditioning with a rituximab-based conditioning regimen. Of these patients, 50 were diagnosed with CLL and were treated on a single arm phase-II clinical trial for CLL trial (NCT00104858) and the other 5 were diagnosed with small lymphocytic lymphoma (SLL) trial (NCT00867529) and were treated on a separate phase-II study focused on lymphoma patients. Both cohorts are collectively included in this analysis (rituximab cohort). We compared the outcome of the 55 patients with that of 157 patients who were transplanted at our institutions between 1997 and 2014 and did not receive rituximab (historical control) (16). Protocols were approved by the institutional review boards of the Fred Hutchinson Cancer Research Center and the collaborating sites. All patients signed consent forms.

Current Patients

Patients with a diagnosis of CLL and SLL were included if they: 1) failed to achieve at least partial response (PR) after at 2 cycles of treatment with a fludarabine containing regimen (or another nucleoside analog) , 2) experienced relapse within 12 months after completing a fludarabine containing regimen, 3) failed FCR (fludarabine, cyclophosphamide and rituximab) regimen at any time or 4) had a deletion on the short arm of chromosome 17 (del17p) and were treated with at least one line of treatment. Patients with active infections, CNS involvement or significant limitations in organ functions were excluded.

Donors

Both HLA-matched related and unrelated donors were allowed. All donors were HLA matched at the allele level at HLA-A, -B, -C, -DRB1, and -DQB1. For unrelated donors a single allele disparity was allowed for HLA-A, B, or C as defined by high resolution typing. Only G-CSF mobilized peripheral blood mononuclear cells (PBMC) were used as a hematopoietic cell source.

Study Design and Treatment

In the single-arm phase-II study, transplants were performed in the outpatient setting and patients were only admitted to inpatient services if medically indicated for control of complications or for the infusion of donor PBMC if overnight infusion was logistically required. Conditioning began four days before HCT.

From days –4 to –2 patients received fludarabine (30 mg/m^2/day i.v.). On day 0, 200 cGy of total body irradiation (TBI) was administered at 6-10 cGy/min from a linear accelerator. PBMC were infused as soon as possible following TBI. Patients received rituximab at a dose of 375 mg/m^2 on day -3 before and days +10, +24, and +38 after HCT. GVHD prophylaxis included cyclosporine (CSP) and mycophenolate mofetil (MMF). CSP was started on day -3 at 5.0 mg/kg orally every 12 hours. In the absence of acute GVHD, CSP was continued until day +56 for related and until day +100 for unrelated recipients followed by taper to day +180. The CSP trough levels were kept at 400 ng/ml until day 28 and 120-360 ng/ml after day 28. MMF was started within 4-6 hours HCT at a dose of 15 mg/kg orally. In patients with related donors, MMF was stopped abruptly on day +27, while for unrelated recipients it was tapered from day +40 until day +96.

Historical Controls

For historical comparison, we included data from all patients who underwent HCT for CLL or SLL on previous prospective and registered trials between 1997 and 2014 (16). The conditioning regimen consisted of fludarabine 30 mg/m^2/d days -4 to -2 followed by TBI (200 or 300 cGy) on day 0. GVHD prophylaxis consisted of a calcineurin inhibitor in addition to MMF as described above. These patients will be referred to as historical cohort.

Statistical Analysis

Cumulative incidences of relapse and NRM and Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) were calculated at 3 years for the rituximab cohort and historical cohort separately. This cut-off was chosen because of the shorter follow-up for the rituximab cohort. Associations between clinically relevant factors and clinical outcomes were assessed using univariate and multivariate cox proportional hazard models. All patients from both the rituximab and the historical cohort were included and contributed to the model (n=215). Factors associated with at least one endpoint at the level of significance of 0.05 from the univariate models were included in the multivariate analysis. These models tested the following factors: age, donor type, CD34+ and CD3+ doses, disease status, diagnosis to transplant interval, numbers of prior treatments, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (> 5cm), fludarabine refractory disease, peri-transplant rituximab and high risk cytogenetics (table-3). High risk cytogenetics were defined as presence of either del17p or a complex (defined as 3 or more abnormalities) karyotype as detected by either analysis of G-banded chromosomes or by fluorescent

in site hybridization. Multivariable models were done separately for patients with high risk cytogenetics. (Table 4).

Results

Patient characteristics:

Pre-transplant characteristics are summarized in table-1. Rituximab patients and historical patients had the following statistically significant differences at baseline: Rituximab patients more frequently had del17p (54% versus 18%, $p<0.001$) or complex cytogenetics (37% versus 18%, $p=0.004$) and more frequently received grafts from unrelated donors (69% versus 48%, $p=0.008$). Additionally, there was a suggestion that they had higher incidences of bulky lymph nodes (26% versus 14%, $p=0.07$) and of HCT-CI scores of ≥3 (47% versus 34%, $p=0.08$), respectively.

Outcomes:

Rituximab patients had a comparable CR rate of 44% compared to 48% among historical patients ($p=0.59$). However, the rate of progression/relapse at 3-years was statistically significantly lower among Rituximab than historical patients (17% versus 31%, $p= 0.04$). There were no statistically significant differences in the unadjusted rates of OS (53% versus 50%, $p=0.85$), PFS (44% versus 42%, $p=0.63$), or NRM (38% vs. 28%; $p=0.20$) between the two groups of patients. (**Figures 1A-D**).

Given the strong association between the HCT-CI and the clinical outcomes, we separately analyzed the outcomes among patients without comorbidities (HCT-CI = 0). The 1-year and 3-year OS rates were 100% and 75% among rituximab patients and 77 % and 63%, respectively, among the historical patients. NRM rates were 0% and 13% for rituximab and historical patients, respectively.

Toxicities:

There was no difference in the rate of grade 3-4 neutropenia (% vs. %; p =) or thrombocytopenia (% vs. %; p =) for rituximab patients compared to historical patients. Non-hematologic adverse events (AEs) were similar between the 2 cohorts with hyperbilirubinemia (13% vs. 13%; p =0.9), hypoxia (9% vs. 11%; p =0.71) and elevated creatinine (9% vs. 5%; p=0.28) as most common AEs. Table-2 summarizes details of non-hematologic events in the two groups of patients.

GVHD:

The incidences of grade 2-4 acute GVHD (69% vs. 58%; p=0.53) and grade 3-4 acute GVHD (18% vs. 18%; p=0.98) were not statistically significantly different between rituximab and historical patients. There was also no difference in the incidence of chronic GVHD at 3 years between the two groups (66% vs. 55%; p=0.68).

Causes of death:

Fifty percent of the rituximab patients died. Causes of death included infections (18%), acute GVHD complications (12%), disease relapse or progression (10%), complications of chronic GVHD (6%) and other causes (4%). Among the historical patients, 62.5% died. Causes of death included disease relapse or progression (27%), infections (13%) and complications from acute (6%) or chronic (3%) GVHD. Other deaths were from neurologic events (2.5%), secondary malignancies (2.5%) or other causes (8%). The cause of death was unknown in one patients.

Predictors of clinical outcomes:

In order to identify independent prognostic factors for clinical outcomes, we developed univariate and multivariate models using data from the entire cohort of patients (n=212). In the multivariable models (**Table 3**), peri-transplant rituximab (HR 0.34, *p*=0.006) and unrelated grafts (HR 0.37, *p*=0.0007) were significantly associated with a lower relapse rate, while high-risk cytogenetics increased the risk of relapse (HR: 4.61, *p*<0.0001). HCT-CI scores of ≥3 were the only predictor for increased NRM (HR 3.63, p=0.001). None of these factors significantly predicted OS with exception for a suggestive association with HCT-CI scores of ≥3 (HR: 1.62, *p*=0.06). Unrelated grafts predicted improved PFS (HR: 0.69, *p*=0.05) while high-risk cytogenetics predicted worse PFS (HR: 1.84, *p*=0.004).

We looked specifically for prognostic markers in patients with high-risk cytogenetics as they are more likely to be offered HCT in the era of novel agents. Among those patients (**Table 4**), having an unrelated donor was associated with both better PFS (HR: 0.38, *p*=0.003) and lower relapse (HR: 0.21, p=0.0003). Peri-transplant rituximab was associated with a lower relapse rate (HR: 0.42, *p*=0.04). Higher HCT-CI was associated with higher NRM.

Discussion

CLL patients with high-risk cytogenetics continue to have relatively poor outcomes with elusive chances of cure. In the current phase-II study, we showed that the addition of 4 doses of peri-transplant rituximab to our traditional minimal-intensity conditioning regimen before HCT resulted in a 3-fold decrease in relapse rates. This benefit was also present among patients with high-risk cytogenetics. Our study confirms previous reports by us and others indicating high long-term PFS and OS rates in patients with high-risk CLL after HCT. (1, 15-17) Likewise, unrelated grafts achieved better disease control supporting the use of such grafts to treat high-risk CLL. In addition, CLL patients with no comorbidities experienced a 3-fold lower incidence of NRM compared to those with multiple comorbidities. While patient numbers were relatively small, most CLL patients (75%) with no comorbidities given rituximab-based conditioning regimen were disease free at 3-years. This suggests that HCT should strongly be considered as treatment of choice for high-risk CLL patients without comorbidities. Recent clinical practice guidelines by the American Society of Blood and Marrow Transplantation (ASBMT) and international workshop on CLL (iwCLL), recommend allogeneic HCT for high-risk CLL patients with refractory disease while they are still responding to either BCR inhibitors or venetoclax.(12-14) Our finding supports that recommendation, especially for patients with no comorbidity.

Addition of rituximab was feasible, improved clinical efficacy and was independently associated with a lower relapse rate both in the entire cohort and in patients with high-risk cytogenetics. More than half of the patients were alive at 3 years and more than 40% were alive without disease progression. Rituximab patients had more comorbidities than historical patients which might explain their slightly higher NRM and comparable OS despite the lower relapse rate seen with rituximab. Our findings are in line with recent reports indicating an independent association between high risk cytogenetics (del17p or complex karypote) and a higher relapse rate and shorter PFS although we did not find an association with OS confirming the findings from the German group. (16, 17)

We believe that HCT remains a viable treatment option for CLL in the era of novel agents. Even with the introduction of new drugs, CLL remains incurable and the duration of response to the novel agents is limited. Ibrutinib – the most effective drug for high-risk CLL to date – provides a median PFS duration of 26 months in patients with del17p based on the longest published follow-up.(8) Similar PFS (27 months) has recently been reported in CLL patients with del17p who were treated with venetoclax.(9, 18) While these results are significantly better than the historical treatments (19) , they also indicate that cure of high-risk CLL using non-transplant approaches remains an unmet need. Moreover, reports from several groups have shown dismal outcomes after ibrutinib or venetoclax failure with reported survivals ranging

from 3 to 18 months, especially in patients who develop Richter's transformation.(6, 7, 20) Also, drug tolerability remains an issue in number of patients and has resulted in treatment discontinuation in 30-40% of patients taking ibrutinib or venetoclax based on the "real-world" data.(11, 21)

Despite robust efficacy data for HCT, the higher incidence of NRM compared to non-transplant approaches is the main clinical concern. It is therefore critically important to investigate novel strategies to reduce NRM after HCT. In this context, very encouraging data on statistically significant reductions in both serious acute GVHD and NRM among unrelated HCT recipients have recently been reported using triple GVHD prevention with MMF, CSP and Sirolimus.(22) In addition, and as alternative treatments for high-risk CLL become more effective and safer, it is important to identify patients with a low comorbidity burden for whom upfront HCT with intent of cure should be recommended.

In conclusion, incorporation of rituximab to the conditioning regimen was feasible and effective and this approach should be further investigated by utilizing newer anti-CD20 monoclonal antibodies that have been shown to be superior to rituximab for CLL in the non-transplant setting.(23) Our findings support early utilization of HCT for patients with high risk CLL with no comorbidities. This approach has the potential of prolonged disease control with acceptable risk of treatment-related mortality.

Tables and Figures

Table-1: Patients characteristics	**Rituximab (n=55)**	**Historical cohort (n=157)**	**P-value**	**All patients (n=212)**
Male gender, n (%)	39 (71)	119 (76)	0.47	158 (75)
Race, n (%)				
Caucasian	53 (100)	148 (95)		201 (97)
Others		7 (5)	0.12	7 (3)
Age, Median (range) years	59 (35-74)	57 (38-72)	0.06	58 (35-74)
Diagnosis, n (%)				
CLL	53 (96)	140 (89)		193 (91)
SLL	1 (2)	10 (6)		11 (5)
PLL	1 (2)	2 (1)		3 (1)
Richter's Syndrome		5 (3)	0.30	5 (2)
Years from Diagnosis to HCT				
Median (range)	5.8 (0.3-21.4)	4.9 (0.4-26.9)	0.21	5.0 (0.3-26.9)
Number of Prior Treatments				
Median (range)	4 (1-10)	4 (0-12)	0.92	4 (0-12)
≥ 5 prior treatments, n (%)	19 (35)	51 (33)	0.80	70 (33)
Disease status at transplant, n (%)				
Complete Remission	5 (10)	10 (6)		15 (7)
Partial Remission	10 (20)	56 (36)		66 (32)
Unresponsive	30 (59)	75 (49)		105 (51)
Untreated Relapse	6 (12)	13 (8)	0.14	19 (9)
Cytogenetics, n (% of tested patients)				
del (17p)	29 (54)	26 (18)	<0.0001	55 (27)
del (11q)	11 (20)	28 (19)	0.82	39 (19)
trisomy 12	6 (11)	23 (16)	0.43	29 (14)
del (13q)	18 (33)	61 (41)	0.31	79 (39)
complex	20 (37)	26 (18)	0.004	46 (23)
Donor Type, n (%)				
Related	17 (31)	81 (52)		98 (46)
Unrelated	38 (69)	76 (48)	0.008	114 (54)
HCT-CI				
Median (range)	2 (0-6)	2 (0-9)	0.006	2 (0-9)
HCT-CI ≥ 3, n (%)	26 (47)	51 (34)	0.08	77 (38)
Conditioning Regimen, n (%)				
Fludarabine[1], TBI 2Gy	52 (95)	128 (82)		180 (85)
Fludarabine, TBI 3Gy	3 (5)	7 (4)		10 (5)
TBI 2Gy	0	22 (14)	0.01	22 (10)
Cell transplanted, Median (range)				
CD34+ x 10^6/kg	7.8 (1.5-28.4)	8.1 (1.1-37.8)	0.79	8.0 (1.1-37.8)
CD3+ x 10^6/Kg	2.9 (0.0-42.3)	2.9 (0.0-6.7)	0.77	2.9 (0.0-42.3)
Fludarabine-refractory disease, n (%)	18 (33)	48 (31)	0.77	66 (31)
Lymph node size ≥ 5 cm, n (%)	14 (26)	20 (14)	0.07	34 (18)

Table-2: Patients with Grade 3-4 Adverse Events *- n (%)				
		Rituximab (n=55)	Historical cohort (n=157)	P-value
Hepatic				
	Hyperbilirubinemia	7 (13%)	21 (13%)	0.9
Renal				
	Elevated creatinine	5 (9%)	8 (5%)	0.28
	Tumor lysis syndrome	0	3 (2%)	0.30
Cardiovascular				
	Hypertension	3 (5.5%)	1 (0.5%)	0.02
	Hypotension	2 (3.5%)	6 (4%)	0.95
	Atrial fibrillation	1 (2%)	3 (2%)	0.96
	Venous Thromboembolism	1 (2%)	2 (1%)	0.76
	Cardiopulmonary arrest	1 (2%)	1 (0.5%)	0.43
	Congestive Heart Failure	0	3 (2%)	0.30
	Acute Coronary Syndrome	0	3 (2%)	0.30
Infectious				
	Hepatitis C	1 (2%)	0	0.09
	Encephalitis	1 (2%)	0	0.09
	Pneumonia	1 (2%)	0	0.09
	Febrile neutropenia	1 (2%)	6 (4%)	0.47
	SEPSIS/septic shock	0	5 (3%)	0.18
	Disseminated/invasive fungal infection	0	4 (2.5%)	0.23
Pulmonary				
	Pleural effusion	1 (2%)	4 (2.5%)	0.75
	Dyspnea	1 (2%)	2 (1%)	0.76
	Diffuse alveolar hemorrhage	1 (2%)	1 (0.5%)	0.43
	Hypoxia	5 (9%)	17 (11%)	0.71
Gastrointestinal†				
	Diarrhea	1 (2%)	2 (1%)	0.76
	Bleeding	2 (3.5%)	2 (1%)	0.26
	Anorexia	1 (2%)	0	0.09
	Colitis	0	5 (3%)	0.18
	Nausea and vomiting	1 (2%)	3 (2%)	0.96
Neurological				

	Neuropathy	1 (2%)	1 (0.5%)	0.43
	Insomnia	0	1 (0.5%)	0.55
	Depression	1 (2%)	0	0.09
	Seizure	1 (2%)	1 (0.5%)	0.43
	Syncope	0	3 (2%)	0.30
	Cerebrovascular accident	1 (2%)	0	0.09
* Occurring in ≥ 1% of patients † Unrelated to GVHD				

Table -3 : Multivariable model of association between relevant clinical factors and outcomes in all patients *								
	Overall Mortality (114 events)		PFS (121 events)		Relapse (55 events)		NRM (66 events)	
	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value
Donor								
Related	1.0		1.0		1.0		1.0	
Unrelated	0.87 (0.6-1.3)	0.49	0.69 (0.5-1.0)	0.05	0.37 (0.2-0.7)	0.0007	1.13 (0.7-1.9)	0.66
HCT-CI								
0	1.0		1.0		1.0		1.0	
1-2	1.21 (0.7-2.0)	0.45	1.28 (0.8-2.1)	0.32	0.78 (0.4-1.5)	0. 46	2.24 (1.0-5.1)	0.05
3+	1.62 (1.0-2.6)	0.06	1.52 (0.9-2.5)	0.09	0.59 (0.3-1.2)	0.13	3.63 (1.6-8.0)	0.001
High risk CG **								
No	1.0		1.0		1.0		1.0	
Yes	1.40 (0.9-2.1)	0.13	1.84 (1.2-2.8)	0.004	4.61 (2.5-8.6)	<0.0001	0.89 (0.5-1.6)	0.68
Rituximab								
No	1.0		1.0		1.0		1.0	
Yes	0.94 (0.6-1.5)	0.81	0.78 (0.5-1.2)	0.27	0.34 (0.2-0.7)	0.006	1.42 (0.8-2.5)	0.23

* Following factors were included in the univariate models and only moved to the multivariable model if reached statistical significance ($p < 0.05$) for any endpoint in the univariate models: age, donor type, disease status, CD34+ and CD3+ doses, number of prior treatments, diagnosis to transplant interval, high risk CG, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (> 5cm), fludarabine refractory disease and rituximab-containing conditioning

** del 17p or complex CG (defined as 3 or more abnormalities)

Table - 4: Multivariable model of association between relevant clinical factors and outcomes in patients with high risk CG (del 17p or complex) *

	Overall Mortality (42 events)		PFS (49 events)		Relapse (27 events)		NRM (22 events)	
	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value
Donor								
Related	1.0		1.0		1.0		1.0	
Unrelated	0.63 (0.3-1.2)	0.18	0.38 (0.2-0.7)	0.003	0.21 (0.1-0.5)	0.0003	0.84 (0.3-2.4)	0.74
CD34 dose/kg								
<7.80	1.0		1.0		1.0		1.0	
≥7.80	1.59 (0.8-3.0)	0.16	1.63 (0.9-2.9)	0.10	1.12 (0.5-2.5)	0.79	2.47(1.0-6.4)	0.06
Number of regimens								
0-4	1.0		1.0		1.0		1.0	
5+	1.39 (0.7-2.7)	0.33	1.30 (0.7-2.4)	0.41	1.26 (0.5-2.9)	0.59	1.20 (0.5-3.0)	0.70
HCT-CI								
0	1.0		1.0		1.0		1.0	
1-2	0.96 (0.4-2.3)	0.93	0.76 (0.3-1.7)	0.51	0.27 (0.1-0.8)	0.01	*	0.005
3+	0.88 (0.4-2.0)	0.75	0.72 (0.3-1.5)	0.38	0.31 (0.1-0.8)	0.01	*	0.009
Rituximab								
No	1.0		1.0		1.0		1.0	
Yes	0.94 (0.5-1.8)	0.86	0.80 (0.4-1.4)	0.46	0.42 (0.2-1.0)	0.04	1.64 (0.6-4.2)	0.31

* Following factors were included in the univariate models and only moved to the multivariable model if reached statistical significance ($p < 0.05$) in the univariate models: age, donor type, disease status, CD34+ and CD3+ doses, number of prior treatments, diagnosis to transplant interval, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (> 5cm), fludarabine refractory disease and rituximab-containing conditioning

† HR not estimable due to 0 events in reference category.

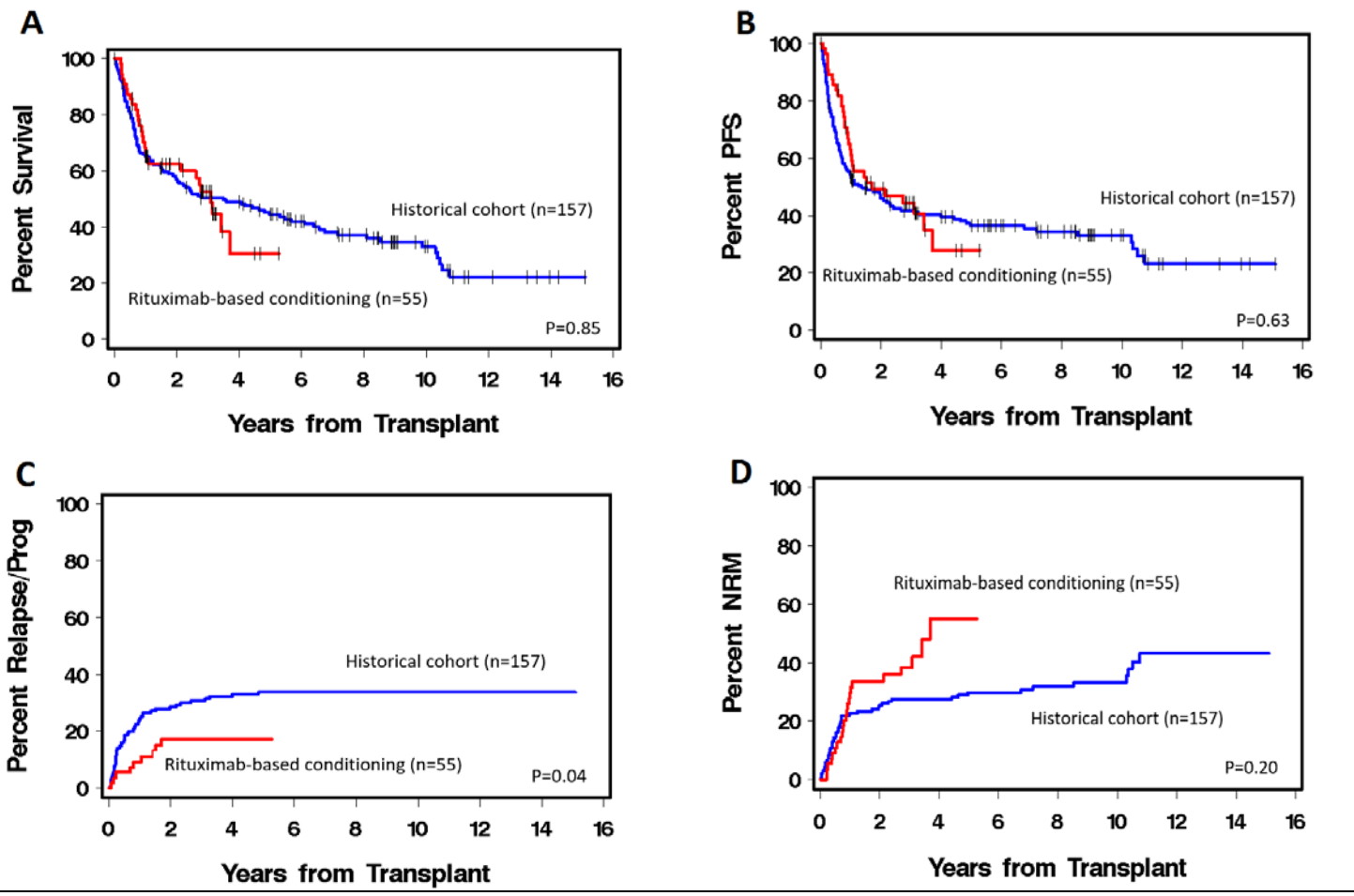

Figure-1: Kaplan–Meier Curves for Overall Survival (A), Progression-free Survival (B), Relapse (C) and non-relapse mortality (D) comparing patients who were treated with rituximab-based conditioning on the phase-II clinical trial (red) and historical cohort patients (blue).
P-values are by log-rank test.

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