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Marie Robin[1], Sylvie Chevret[2], Linda Koster[3], Christine Wolschke[4], Ibrahim Yakoub-Agha[5], Jean Henri Bourhis[6], Patrice Chevallier[7], Jan J Cornelissen[8], Péter Reményi[9], Johan Maertens[10], Xavier Poiré[11], Charles Craddock[12], Gérard Socié[1], Maija Itälä-Remes[13], Harry C Schouten[14], Tony Marchand[15], Jakob Passweg[16], Didier Blaise[17], Gandhi Damaj[18], Zubeyde Nur Ozkurt[19], Tsila Zuckerman[20], Thomas Cluzeau[21], Hélène Labussière-Wallet[22], Jörg Cammenga[23], Donal McLornan[24], Yves Chalandon[25] and Nicolaus Kröger[3]

[1] Hopital Saint-Louis, APHP, INSERM 1131, Paris, France
[2] Service de biostatistique, Hôpital Saint-Louis, APHP, ESCTRA Team, INSERM UMR1153, Université Paris 7, Paris, France
[3] EBMT Data Office Leiden, Leiden, The Netherlands
[4] University Hospital Eppendorf, Hamburg, Germany
[5] CHU de Lille, LIRIC, INSERM 995, université de Lille, 59000 Lille, France
[6] Institut Gustave Roussy, INSERM U1186, Université Paris Saclay, Villejuif, France
[7] CHU Nantes, Nantes, France
[8] Department of hematology, Erasmus University Medical Center, Rotterdam, The Netherlands.
[9] St. István & St. Laszlo Hospital, Budapest, Hungary
[10] University Hospital Gasthuisberg, Leuven, Belgium
[11] Cliniques Universitaires St. Luc, Brussels, Belgium
[12] Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham, UK
[13] HUCH Comprehensive Cancer Center, Helsinki, Finland
[14] University Hospital Maastricht, Maastricht, The Netherlands
[15] Centre Hospitalier Universitaire de Rennes, Rennes, France
[16] University Hospital, Basel, Switzerland
[17] Aix-Marseille Univ, Inserm, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France
[18] CHU CAEN, Caen, France
[19] Gazi University Faculty of Medicine, Ankara, Turkey
[20] Rambam Medical Center, Haifa, Israel
[21] Universisté Cote d'Azur, CHU Nice, INSERM U1065, Nice, France
[22] Centre Hospitalier Lyon Sud, Lyon, France
[23] University Hospital, Linköping, Sweden
[24] Comprehensive Cancer Centre, Department of Haematology, Kings College, London
[25] Hôpitaux Universitaires de Genève and Faculty of Medicine, University of Geneva, Geneva, Switzerland

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Correspondence: Marie Robin at marie.robin@aphp.fr
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Abstract

Antihuman T-lymphocyte immunoglobulin is still much debated in the setting of transplant from an HLA matched related donor. Acute and chronic graft-versus-host disease are the main cause of morbidity and mortality after allogeneic hematopoietic stem cell in patients with myelofibrosis. The aim of this study was to evaluate the effect of antihuman T-lymphocyte immunoglobulin in a large cohort of patients with myelofibrosis. 287 patients were included in the study. Cumulative incidence of grade 2-4 acute graft-versus-host disease was 26% and 41% with or without antihuman T-lymphocyte immunoglobulin. Chronic graft-versus-host disease incidence was 52% and 55%. Non-adjusted overall Survival, Disease Free Survival and non-relapse mortality were 55% vs 53%, 49% vs 45%, and 32% vs 31%, respectively with or without antihuman T-lymphocyte immunoglobulin. An adjusted model confirmed that acute graft-versus-host disease risk was lower following antihuman T-lymphocyte immunoglobulin (Hazard ratio : 0.54, p=0.010) whilst it did not decrease the risk of chronic graft-versus-host disease. Hazard ratio for overall survival and non-relapse mortality were 0.66 and 0.64, with p-value at 0.05 and 0.09, respectively. Antihuman T-lymphocyte immunoglobulin did not influence disease-free survival, graft-versus-host disease and relapse free survival and relapse risk. In conclusion, in the setting of matched related transplantation in myelofibrosis patients, this study demonstrates that antihuman T-lymphocyte immunoglobulin decreases acute graft-versus-host disease risk without increasing relapse risk.

Article summary

- This study from EBMT registry explores the role of ATG in myelofibrosis patients who underwent an HLA-matched related donor transplantation
- Acute GVHD was decreased with ATG but not chronic GVHD and DFS was similar with or without ATG

Introduction

Primary myelofibrosis (MF) or MF secondary to Polycythemia Vera or Essential Thrombocythemia are myeloproliferative neoplasms characterized by progressive fibrosis of the marrow and myeloid metaplasia in the spleen and the liver. Disease severity can be assessed by a number of different prognostic scoring systems, able to predict survival without treatment in patients with both primary or secondary MF [1–5]. Usual risk factors taken into account within these scores are disease-related symptoms, the degree of cytopenia or hyperleucocytosis, peripheral or marrow blast excess and age. Moreover, cytogenetics and somatic mutations provide additional prognostication power to these scoring tools[3,6–9]. According to the number of risk factors, median expected survival from diagnosis can range from more than 10 years to less than 18 months. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment in patients with MF. One registry based study demonstrated that patients with Dynamic International Prognostic Scoring System (DIPSS) intermediate-2 or high risk disease have an advantage in overall survival (OS) following transplantation strategies and international expert consensus guidelines are in favour of transplant in these patients [10,11]. Cumulatively, overall survival (OS) after HSCT can range between 40 and 65% according to risk factors related to disease, patient and type of donor[12–18]. Results have been considered better with transplant from a HLA-matched sibling donor than an unrelated donor. However, acute and chronic GVHD remain frequent causes of death in patients with MF undergoing HSCT, often contributing to a relatively high transplant-related mortality of around 30%[12–18]. The optimal conditioning regimen and GVHD prophylaxis approach in these patients remains unknown. Two prospective studies of HSCT in MF, in which the conditioning regimen and GVHD prophylaxis strategies were homogeneous, can be detailed to compare GVHD rates and outcomes. In 2009, Kröger *et al* reported on 103 MF patients conditioned by fludarabine, busulfan and antihuman T-lymphocyte immune Globulin Grafalon® at 30mg/kg using a matched related donor and at 60 mg/kg for an unrelated donor, combined with cyclosporine and short course of methotrexate. With this regimen including *in vivo* T-cell depletion approach, the acute grade 2-4 GVHD rate was relatively low (27%) and chronic GVHD incidence was 49%. Relapse incidences were 32% in the setting of a matched related donor and 20% with an unrelated donor (not significantly different). Rondelli et al, subsequently reported on a second prospective trial for MF HSCT using a fludarabine and melphalan platform in patients transplanted from a matched related donor, with the addition of Thymoglobulin® in patients with an unrelated donor[17]. Acute GVHD rates were significant at 38% and 41%, in the sibling group and unrelated group respectively. Chronic GVHD rates did not differ significantly between the sibling (36%) and unrelated donor (38%) setting. Of particular note,

mortality was dramatically higher (68%) in the group of patients who underwent unrelated donor HSCT but the effect of ATG on this higher mortality risk remains undetermined. Collectively, from these 2 studies, we can see that in the matched related setting, it is not obvious to conclude ATG is beneficial. Recently, a randomized trial has shown that ATG prevents chronic GVHD in the setting of HLA-matched sibling donor for acute lymphoid leukemia or acute myeloid leukemia following myelo-ablative conditioning regimens (MAC)[19]. Indeed, while acute GVHD was non-significantly lowered, the cumulative incidence of chronic GVHD dropped from 69% without ATG to 32% with Grafalon® without increasing the relapse risk. In this large EBMT cohort, we aimed to determine the effect of ATG in the setting of HSCT for MF using a HLA-matched sibling donor, which is of particular importance as data remains scarce given the rarity of the disease.

Methods

Consecutive patients transplanted from a matched sibling donor without *ex vivo* graft manipulation between 2007 and 2015 for MF and registered in the EBMT registry were included in this study. Patients who received post transplant cylocphosphamide, alemtuzumab and those without sufficient information regarding blood cell counts prior to transplantation were excluded. A total of 287 patients were selected for the final analysis, amongst whom a total of 135 received *in vivo* T-cell depletion while 152 did not.

DIPPS was calculated according to the original definition[1]. Some patients had missing data for peripheral blast count at transplant, in these cases, the blast count was taken at diagnosis. General symptoms were either weight loss or sweat (only 2 patients had fever), 50 patients had missing data for constitutional symptoms. Because the brand of drug used for T-cell depletion was not available in the registry, a stepwise hypothetical strategy was formulated to identify patients who received thymoglobulin® and those who had received grafalon®: ATG dosages at 10 mg/kg or lower were considered as thymoglobulin® whereas dosages at 20 mg/kg or higher were considered as grafalon® based on usual doses in each brand. This was also checked by country where the HSCT occurred, as some countries used only grafalon®, others used thymoglobulin and some both products.

DFS was defined as survival without disease relapse or progression documented in the registry. GVHD relapse-free survival (GRFS) was defined as survival without disease relapse or progression, without grade 3-4 acute GVHD and without chronic extensive GVHD documented in the registry.

Analysis of failure time data used Kaplan Meier estimates, log-rank tests and Cox modeling unless competing risks existed, whereby cumulative incidence curves, Gray's test and cause-specific Cox

models were used, respectively[20]. In estimating cumulative incidence of chronic GvHD, patients were censored at the time of DLI, as previously reported. Based on frailty models [21], we tested whether there were center effect on each outcome.

The study complied with regulatory requirements, the declaration of Helsinki and Good Practice standards. Independent review board approved the study. Patients gave written informed consent.

Results

Patients and transplant characteristics

Main patient, disease and transplant characteristics are described in **Table 1**. Median age was 56.9 years [IQR, 50.6- 61.5], ranging from 22.1 up to 75.5 years. There was a majority of male patients (68%). Patients without (n=152) or with ATG (n=135) had similar characteristics regarding age, gender, type of MF (primary or secondary) but differed for other characteristics including splenectomy before transplant (38% vs. 9%), DIPSS score (int-2 or high: 59% vs. 68%), conditioning regimen (**Table 1**) and source of stem cells (marrow 17% vs. 2%). More patients in the ATG-group received calcineurin inhibitors alone (26% vs. 7%).Concerning pre-transplant therapy, 5 patients in the non-ATG cohort and 14 in the ATG cohort received the JAK inhibitor ruxolitinib (Novartis Pharmaceuticals, Geneva, Switzerland). Regarding the brand of ATG used, in the ATG-group, 37 patients received Grafalon®, 96 received Thymoglobuline® and the brand was undetermined for 2 patients.

Engraftment

Six patients had primary graft rejection (3 in the ATG and 3 in the non-ATG cohort). Four of these patients received a second HSCT and 3 of them were alive and in remission at the time of last reported follow-up. Cumulative incidence of neutrophil engraftment at day 60 was 96.3% (95%CI, 90.9-98.5) and 94.1% (95%CI, 88.7-96.9) without or with ATG (p=0.35). Cumulative incidence of platelet recovery was 68.4% (95%CI: 60.3-75.2) and 80.3% (95%CI: 72.3-86.1) without and with ATG (p=0.09) at 6 months. Twenty-four patients (14 ATG and 10 non-ATG) had a secondary rejection at a median time of 9 months following HSCT and all but one had disease progression. Half of them received a second HSCT, which failed to achieve a remission.

Outcome

Median time to onset of acute GVHD was 36 days. Cumulative incidence of grade II-IV acute GVHD was significantly higher without ATG: 41.4% (95%CI: 33.1-49.5) versus 26.2% (95%CI: 18.7-34.3) (p=0.0067) whereas the incidence of grade III-IV GVHD was similar in both groups (**Figure 1**). Median time to develop chronic GVHD was 198 days. The incidence of chronic GVHD was high > 50% for both groups of patients (**Figure 1**) without any significant differences according to ATG. Rates of chronic extensive GVHD were also similar in both groups. Cumulative incidence of relapse was 24.4% (95%CI: 16.5-33.1) after ATG and 18.6% (95%CI: 12.1-26.1) without ATG (p=0.083). Non-relapse mortality was 32.5% (95%CI: 24.4-40.7) with ATG versus 31% (95%CI: 20.9-41.6) without ATG. During the follow-up period, a total of 65 non-ATG patients and 44 ATG-patients died. The primary cause of death was related to MF progression in 34% non-ATG and 29% in ATG –patients, respectively. The 5-year OS (54.7% vs. 52.8%), disease-free survival (DFS) (49% vs 44.7%), and GRFS (29.3% vs 23.6%) were not significantly different on univariate analysis (**Table 2)**

Effect of ATG

Due to disparities between ATG and non-ATG group, univariate analysis gave no clue on ATG effect. A multiple variable model was generated to analyse the potential role of ATG on outcome (**Supplementary table 1S**). Age was the strongest variable significantly associated with OS, DFS, and NRM. Adjustment was made on age at transplant, Lille score, Karnofsky performance status score, splenectomy before transplant, intensity of conditioning regimen (RIC versus MAC) and source of stem cells (marrow versus peripheral blood). There was no centre effect for any outcome (**Supplementary Table 2S**). **Table 3** shows the ATG effect for each outcome. Hazard ratio (HR) favoured ATG for OS (HR: 0.66, 95%CI: 0.43-1.00, p=0.05) and NRM (HR: 0.64, 95%CI: 0.39-1.07, p=0.09). Grade II to IV acute GVHD was significantly lower with ATG (HR: 0.54, 95%CI: 0.34-0.86, p=0.01) but this was not the case for either grade III-IV acute GVHD or chronic extensive GVHD. In this model, ATG had no significant impact on DFS, GRFS or relapse risk (see values in **Table 3**). Taken into account variables of the adjusted model, **Figure 2** shows OS, DFS and GRFS.

Discussion

While there is some evidence that *in vivo* ATG can be protective from acute and chronic GVHD occurrence, which may translate into a higher probability of GRFS in patients transplanted from an HLA matched related donor[19], no specific data in patients with MF undergoing HSCT exists, due to its low patient numbers. In this retrospective study on behalf of the EBMT group, we analysed the impact of ATG in the largest documented cohort of patients with MF transplanted with a HLA-matched related donor. Approximately half of patients received ATG which is higher than previously reported by the CIBMTR registry where only 11% of patients with a matched related donor received ATG[22]. ATG was less frequently used before 2010 (35% vs 51%). The majority of patients received a reduced intensity conditioning regimen and the preferred source of stem cells was peripheral blood. Our study demonstrated that acute GVHD was decreased following ATG but there was no impact on chronic GVHD. The lack of attenuated chronic GVHD risk is in contrast to the findings of the randomized trial comparing ATG versus non-ATG in the setting of matched related donor HSCT published recently by Kröger et al[19]. However, this study included patients with acute leukaemia who underwent MAC-platforms whereas our study included predominantly RIC regimens and focused only on MF. Of note, the rates of acute GVHD, even in patients who received ATG was relatively high in our cohort (26%) as compared to the prospective study cited above but not dissimilar from other studies including only MF patients[17,18]. Rates of chronic GVHD were significantly high even after ATG, indeed higher than previously reported in this disease setting. The question whether these MF-patients are more susceptible to develop chronic GVHD is thus raised. We could postulate that these patients, who still have MF slowly resolving in the first months after transplantation have a pro-inflammatory profile able to trigger GVHD. Indeed, MF is associated with elevated pro-inflammatory biomarkers associated with both auto-immune disease or immune dysregulation [23–26] and it has been demonstrated that the marrow remains fibrotic at 3 months following HSCT in approximately half of patients[27]. Moreover, Hussain et al reported that even in cases of fibrosis resolution following HSCT, pro-inflammatory cytokines and tissue remodelling factors can remain elevated [28]. In contrast, other cytokines remain downregulated following HSCT, such as the T-cell inhibitory receptor Tim-3 (T-cell immunoglobulin and mucin-domain containing-3), which may play a role in GVHD control [28,29].

While ATG clearly decreased the risk of acute GVHD, the adjusted model showed a trend towards improved OS in patients who received ATG (p=0.05). This higher risk of mortality may be explained by higher risk of acute GVHD even if the excess of mortality was not observed only in the first months post-transplant corresponding to GVHD. Treatment of GVHD and steroid refractory GVHD may contribute to mortality in patients who did not receive ATG. Of note, the definition of acute and chronic GVHD in the registry was still restricted to the chronological definition where GVHD occurring

the 100 first days was considered as acute GVHD but we had no data regarding late acute GVHD which is considered as chronic GVHD in this study. Indeed, the classification of acute and chronic GVHD was not done according to the latest National Institute of Health (NIH) consensus and indeed chronic GVHD may be overestimated because through inclusion of late acute GVHD[30]. Our analysis was based on registry data and GVHD was not recoded at posteriori according to NIH classification. The analysis of GRFS which captures both severe acute and severe chronic GVHD is an important endpoint in this setting, showing no difference with or without ATG. Of note, even if the risk of chronic GVHD is mostly influenced by a previous acute GVHD, other variables like immunosuppressive therapy management and cellular therapy may interfere in chronic GVHD risk. Finally, this is the first study which shows a trend to lower mortality using an ATG approach. Four prospective trials conducted in the unrelated setting and the aforementioned study in the matched sibling donor setting, have not reported a significant advantage in overall survival with ATG[19,31−33]. In contrast, one large prospective randomized trial has reported lower OS in patients receiving ATG in the setting of unrelated donor (RIC or MAC)[34]. It must be considered however that the dosing of ATG and their manufacturing process may also have an impact on outcome and differ in the various prospective trials. In the present EBMT study, we could identify patients who received thymoglobulin® or Grafalon® but due to small subgroup numbers, we could not make conclusions on individual products regarding their specific impact on outcome (data not shown). Absolute lymphocyte count may also contribute to ATG efficiency which could not be studied here through the registry[34]. We can just postulate that MF patients, who are usually naïve of intensive chemotherapy may arrive for transplantation with subnormal lymphocyte count, which can be targeted by ATG. Regarding relapse risk, it was not confirmed in the multivariable model that ATG increased the risk of relapse however relapse continued to occur late after HSCT without a real plateau highlighting the importance of long-term monitoring in MF patients who received an HSCT.

In conclusion, this retrospective data analysis of MF patients undergoing HSCT registered in the EBMT registry confirms that *in vivo* ATG is able to protect against acute GVHD and possibly may decrease mortality rates. A prospective study is needed to confirm the role of ATG in MF patients transplanted from an HLA-matched related donor.

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Table 1. Patient and transplant characteristics

	No ATG	ATG	P value
Total number	152	135	
Median age (IQR)	56 (50-61)	58 (51-62)	0.07
Recipient gender			0.53
Male (%)	100 (66)	94 (70)	
Female (%)	52 (34)	41 (30)	
Median time from diagnosis to transplant in months (IQR)	41 (15-120)	30 (9-84)	0.13
Disease			0.07
Primary myelofibrosis (%)	97 (64)	83 (61)	
Secondary myelofibrosis (%)	44 (29)	50 (37)	
Transformation into AML (%)	11 (7)	3 (2)	
Date of transplantation			
Before 2010	52 (34)	29 (21)	
2010 and after	100 (66)	106 (79)	0.02
Splenectomy before transplant (%)	42 (38)	12 (9)	<0.0001
Lille score			0.58
Low	30 (20)	31 (23)	
Intermediate	78 (51)	58 (43)	
High	44 (29)	46 (34)	
DIPSS score			0.018
Low	21 (18)	6 (6)	
Intermediate-1	27 (23)	24 (25)	
Intermediate-2	45 (39)	32 (34)	
High	23 (20)	32 (34)	
Missing	36	41	
Conditioning regimen			P< 0.0001
TBI-cyclophosphamide or fludarabine	30 (20)	2 (1.5)	
Busulfan-cyclophosphamide	18 (12)	2 (1.5)	
Fludarabine-busulfan*+/-other	37 (24)	110 (81)	
Fludarabine-melphalan+/-other	62 (41)	14 (10)	

FLAMSA	3 (2)	7 (5)	
Fludarabine-thiotepa	2 (1)	0	
GVHD prophylaxis			<0.0001
Calcineurin inhibitor alone	8 (5)	39 (29)	
Calcineurin inhibitor and methotrexate	63 (42)	47 (35)	
Calcineurin inhibitor and MMF	75 (49)	46 (34)	
Other	4 (3)	3 (2)	
Missing	1 (0.6)	0	
Recipient CMV serostatus			0.90
Positive	95 (63)	82 (61)	
Negative	57 (37)	52 (39)	
Missing	0	1	
Conditioning regimen			
Reduced intensity	115 (76)	113 (84)	0.11
TBI based	39 (26)	3 (2)	<0.0001
Source of stem cells			<0.0001
Marrow	26 (17)	3 (2)	
Blood	126 (83)	132 (98)	
Gender			0.38
Male recipient / Female donor	37 (24)	44 (32)	
Male recipient / Male donor	63 (41)	50 (37)	
Female recipient / Female donor	21 (14)	20 (15)	
Female recipient / Male donor	31 (20)	21 (16)	
Karnosfsky score, median [range]	90 [80-100]	90 [80-100]	
80% or more, n (%)	142/147 (96%)	116/124 (93%)	0.27

Table 2. Outcome in patients with or without T-cell depletion (univariate)

Outcomes: number of events	No ATG (n=152)	ATG (n=135)	P value
Neutrophil recovery 60-day cum incidence	143 94.1% (88.7-96.9)	130 96.3% (90.9-98.5)	Gray: p=0.35
Platelet recovery 180-day cum incidence	104 68.4% (60.3-75.2)	108 80.3% (72.3-86.1)	Gray: p=0.09
Grade II-IV acute GvHD 4-mo cum incidence	58 41.4% (33.1-49.5)	32 26.2% (18.7-34.3)	Gray: p=0.0067
Grade III-IV a GVHD 4-mo cum incidence	18 11.9% (7.3-17.6)	20 15.1% (9.6-21.7)	Gray : p=0.47
Chronic GVHD* 5-year cum incidence	75 51.7% (43.1-59.6)	62 54.6% (44.5-63.7)	Gray: p=0.47
Extensive chronic GVHD * 5-year cum incidence	37 25.8% (18.9-33.3)	33 28.3% (20.4-36.7)	Gray: p=0.50
Relapse 5-year cum incidence	24 18.6% (12.1-26.1)	29 24.4% (16.5-33.1)	Gray: p=0.083
Non-relapse mortality 5-year cum incidence	45 32.5% (24.4-40.7)	31 31.0% (20.9-41.6)	Gray: p=0.56
Death Median (95%CI) 5-year OS	65 63.4 months (39.8-NA) 54.7% (45.1-63.1)	44 64 months (44.7-NA) 52.8% (42.1-66.3)	Logrank p=0.43
Cause of death Relapse/progression Other Unknown	 22 (34%) 35 (54%) 8 (12%)	 13 (29%) 28 (64%) 3 (7%)	Fisher exact: p=0.52
Relapse or death Median (95%CI) 5-year DFS	69 59.5 months (29-NA) 49.0% (40.6-59.0)	60 38.1 months (23.6-NA) 44.7% (34.7-57.4)	Logrank: p=0.46
GVHD relapse death Median (95%CI) 5-year GRFS	95 9.9 months (8.2-17.7) 29.3% (22.0-38.9)	86 7.5 months (6.7-11.3) 23.6% (15.8-35.2)	Logrank: p=0.12

*censored at DLI

Table 3. Adjusted effect of ATG for NRM, OS, DFS, GRFS, relapse, GVHD; adjustment on age at transplant, Lille score, Karnofsky performance status, splenectomy, conditioning regimen intensity and source of stem cells.
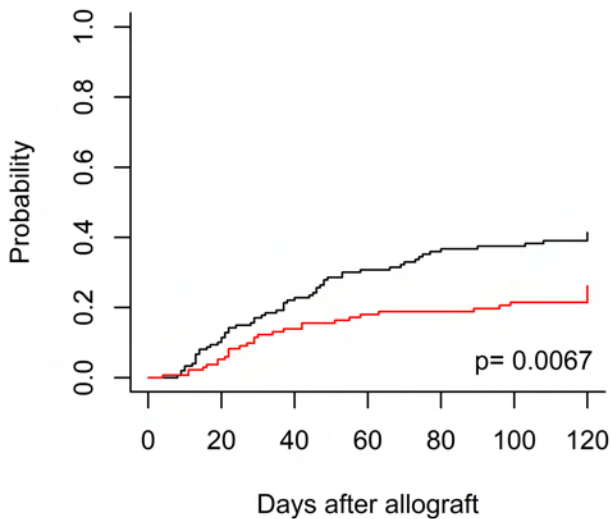
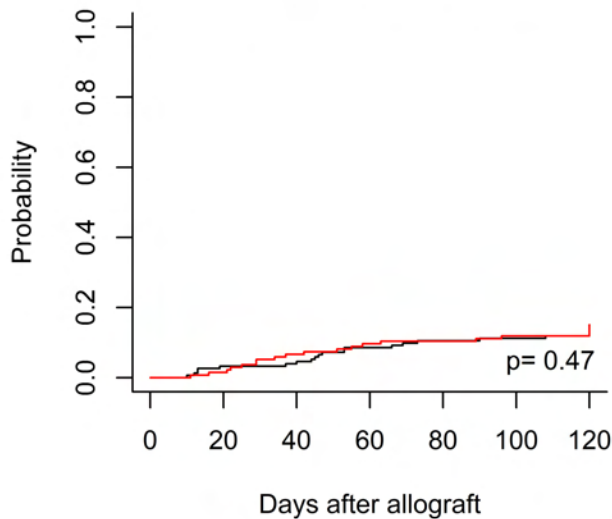|	Hazard Ratio (96% CI) ATG versus none	P-value
OS	0.66 (0.43-1.00)	0.05
Relapse	1.31 (0.71-2.42)	0.39
NRM	0.64 (0.39-1.07)	0.09
Grade 2-4 acute GVHD	0.54 (0.34-0.86)	0.01
Grade 3-4 acute GVHD	1.11 (0.54-2.28)	0.77
Chronic ext GVHD	1.17 (0.72-1.91)	0.52
DFS	0.86 (0.59-1.27)	0.46
GRFS	1.05 (0.76-1.46)	0.74

Figure legends.

Figure 1. Acute and chronic GVHD. Top panels represents incidences of grade 3-4 and grade 3-4 acute GVHD. Down panels represent incidences of chronic GVHD and chronic extensive GVHD.

Figure 2. Adjusted survivals curves. From left to right, OS, DFS, GRFS in ATG-patients (red) and non-ATG (black) with confidence interval (dotted line). Curves have been adjusted according to multiple Cox models.
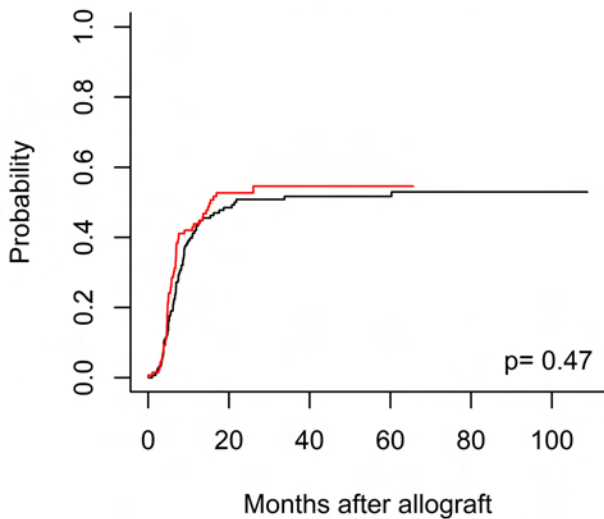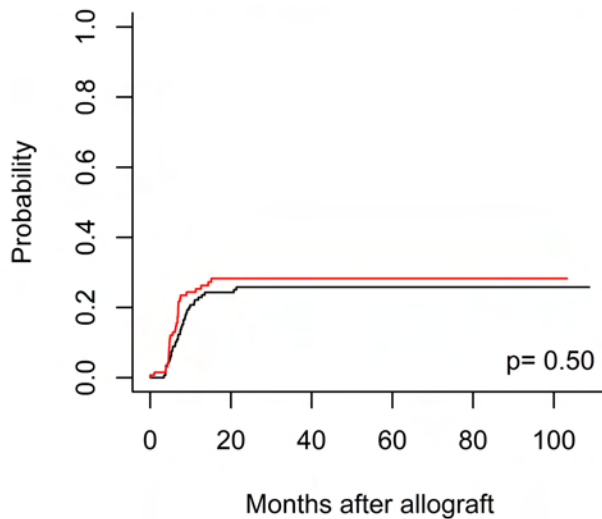
Acute grade 2-4 GVHD

Probability vs Days after allograft. p= 0.0067
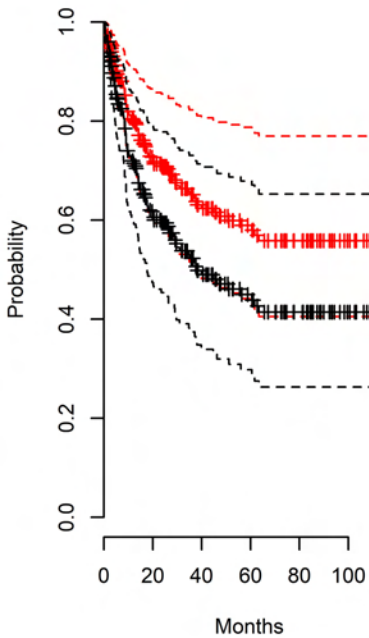
Acute and grade 3-4 GVHD

Probability vs Days after allograft. p= 0.47

Chronic GVHD

Probability vs Months after allograft. p= 0.47

Chronic and extensive GVHD

Probability vs Months after allograft. p= 0.50
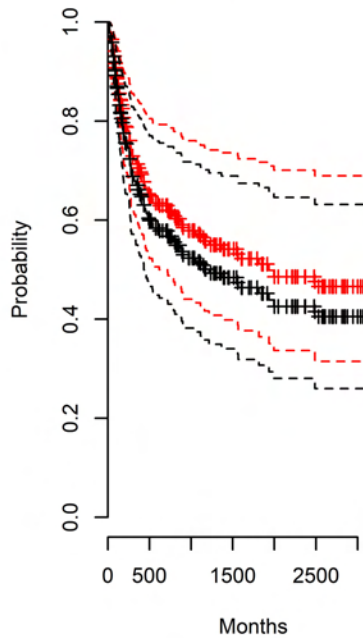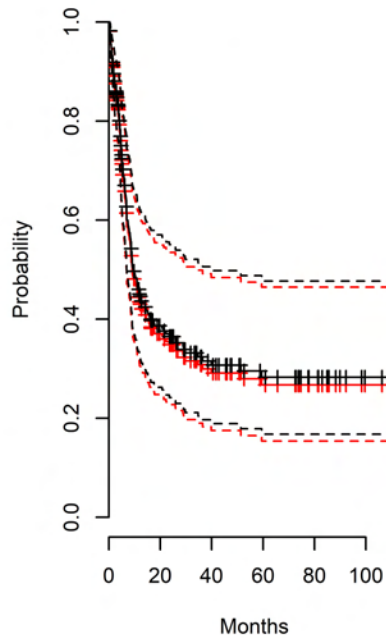
Supplemental tables

Table 1S. Multivariable models

	Overall Survival		Disease Free Survival		Relapse		Non relapse mortality		GRFS	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
ATG	**0.66 (0.43-1.00)**	**0.05**	**0.86 (0.59-1.27)**	**0.46**	**1.31 (0.71-2.42)**	**0.39**	**0.64 (0.39-1.07)**	**0.09**	**1.05 (0.76-1.46)**	**0.75**
Age	1.04 (1.02-1.07)	<0.0001	1.04 (1.01-1.06)	0.001	1.01 (0.98-1.04)	0.60	1.06 (1.03-1.09)	<0.0001	1.03 (1.01-1.05)	0.002
Lille score high	0.72 (0.45-1.16)	0.18	0.77 (0.50-1.20)	0.25	0.86 (0.44-1.70)	0.67	0.73 (0.41-1.30)	0.28	0.95 (0.65-1.39)	0.79
Karnofsky score	0.76 (0.44-1.31)	0.32	0.65 (0.39-1.08)	0.19	0.41 (0.17-0.96)	0.04	0.89 (0.47-1.68)	0.72	0.87 (0.57-1.34)	0.54
Splenectomy	0.98 (0.96-1.00)	0.07	0.99 (0.97-1.01)	0.21	0.98 (0.95-1.01)	0.24	0.99 (0.96-1.02)	0.51	0.99 (0.98-1.02)	0.87
RIC	0.77 (0.45-1.31)	0.34	0.73 (0.44-1.22)	0.23	0.99 (0.46-2.12)	0.98	0.59 (0.29-1.18)	0.14	0.68 (0.45-1.04)	0.07
PB* as source of SC	1.10 (0.65-1.87)	0.71	1.02 (0.62-1.65)	0.95	0.99 (0.46-2.13)	0.99	1.04 (0.55-1.94)	0.91	0.91 (0.61-1.36)	0.64

Peripheral blood stem cells as source of stem cells.

Table 1S. followed.

	Chronic GVHD	
	HR (95%CI)	P-value
ATG	1.19 (0.73 to 1.93)	0.48
Age	1.03 (1.00 to 1.06)	0.021
Lille score high	0.96 (0.54 to 1.69)	0.88
Karnofsky score	1.01 (0.98 to 1.04)	0.40
Splenectomy	0.79 (0.41 to 1.50)	0.47
RIC	0.93 (0.50 to 1.73)	0.82
PB* as source of SC	1.42 (0.59 to 3.41)	0.44

Table 2S. Center effect tested by frailty model

Outcome	Variance of random effect	p-value
Overall Survival	0.0959	0.17
Disease Free Survival	0.106	0.15
Relapse	0.118	0.28
Non relapse mortality	0.248	0.11
Acute GVHD, grade 3 or 4	<0.0001	0.94
Chronic GVHD, severe	0.376	0.083
Relapse GVHD Free Survival	0.028	0.30