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Bone marrow versus mobilized peripheral blood stem cell grafts for non T-cell depleted haploidentical transplants using post-transplant Cyclophosphamide: an ALWP-EBMT analysis.

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Abstract

Incidence of graft versus host disease (GVHD) in the haploidentical transplants using post-transplant Cyclophosphamide (PT-Cy) with bone marrow (BM) grafts is low, while GVHD incidence using mobilized peripheral blood stem cell (PB) ranges between 30% to 40%.

With the aim to evaluate the effect of stem cell source in haploidentical transplant using PT-Cy, we analyzed 451 patients transplanted for AML or ALL reported to the EBMT from 2010 to 2014.

BM was the graft source for 260 patients and PB for 191. Median follow up was 21 months.

Myeloid engraftment was lower in BM recipients (92% vs 95, p<0.001). Use of BM was associated with lower incidence of grade II-IV and grade III-IV acute GVHD (21% vs 38%, p=<0.01; and 4% vs 14%, p=<0.01, respectively). No difference in chronic GVHD, relapse and NRM were found for PB or BM. At 2 year OS was 55% vs 56%, p=0.57, LFS was 49% vs 54%, p=0.74, for BM and PB, respectively.

In multivariate analysis PB was associated with increased risk of grade II-IV (HR 2.1, p<10-4) and grade III-IV aGVHD (HR 3.8, p<0.001).

For LFS and OS, RIC regimen was the only factor associated with treatment failure, (LFS: HR 1.40, p=0.04; OS: HR 1.5, p=0.02) and relapse (HR 1.62, p=0.02).

Center effect, entered as a frailty variable in multivariate model was significant for NRM, LFS, GRFS, OS and cGVHD.

Our study indicates that, in patients with acute leukemia in first or second CR receiving haploidentical transplant with PT-Cy, the use of PB significantly increases the risk of acute GVHD, whereas survival outcomes were comparable.

Introduction

The role of stem cell source in the setting of related or unrelated donor transplant (HSCT) and myeloablative conditioning regimen (MAC) has been evaluated in randomized trials showing an excess of chronic graft versus host disease (GVHD) with peripheral blood stem cell (PB) as the stem cell source (SC), while no differences in disease free and overall survival[1]. Subsequently Eapen et al[2] did not confirmed the increased risk of chronic GVHD with PB grafts, in a registry based study analyzing HSCT with reduced intensity conditioning regimen (RIC) from unrelated donors.

Numbers of unmanipulated haploidentical transplants (haplo SCT) for adult patients with hematological malignancies such as acute myeloid (AML) or acute lymphoblastic leukemia (ALL) are consistently increasing[3]. The Haplo SCT are performed with different conditioning regimen and GVHD prophylaxis[4], with comparable results to HSCT from unrelated donors[5,6].

Historically, Luznik et al[7] pioneered the use of post-transplant Cyclophosphamide (PT-Cy) in the setting of RIC using bone marrow (BM) as stem cell source. This protocol is associated with a low incidence of acute and chronic GVHD and low transplant related mortality also for older patients, while disease recurrence was rather high partially due to the high risk disease in most of the transplanted patients[8].

To overcome the high incidence of relapse with RIC haplo SCT, some authors effectively reported the application of BM and PT-Cy with myeloablative regimes (MAC)[9] and also with the use of PB[10] as stem cell source. Incidence of GVHD in the haploidentical transplants using PB grafts ranges from 30% to 40% in single center report[11].

Recently, O'Donnell et al[12] reported comparable results in recipients of BM versus PB grafts in the non-ablative setting in a matched paired analysis on patients transplanted for several hematological malignancies.

With the aim to analyze the effect of stem cell source in non T-cell depleted haploidentical transplant using PT-Cy, we analyzed patients transplanted for AML or ALL in first or second complete remission (CR) and reported to the EBMT from 2010 to 2014.

Methods

Study design

This is a retrospective registry based analysis on behalf of the ALWP of EBMT.

The EBMT is a voluntary working group of more than 500 transplant centers that are required to report all consecutive stem cell transplantations and follow-up once a year. Audits are routinely performed to determine the accuracy of the data.

All adults (age > 18 years) with ALL or AML in first or second CR (CR1 or CR2) at transplant, reported to Promise-EBMT, who underwent a Haplo-SCT using PTCY as first allogeneic HSCT between 2010 and 2014 were analyzed. Haplo was defined as recipient-donor number of HLA mismatches > 2.

A total of 451 patients were reported from 99 transplant centers, including 260 patients receiving BM and 191 PB as stem cell source.

This study was approved by the ALWP of the EBMT institutional review board. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients or legal guardians provided written informed consent authorizing the use of clinical information for research purposes.

Endpoints and definitions

The primary end point was leukemia free survival (LFS). Secondary end points were neutrophil engraftment, acute GVHD (aGVHD) and chronic GVHD (cGVHD), relapse incidence (RI), non-relapse mortality (NRM), GVHD-free, relapse-free survival (GRFS) and overall survival (OS). Refined GRFS[13] was defined as survival without the following events: grade 3-4 acute GVHD, severe cGVHD, disease relapse, or death from any cause after Haplo-SCT. LFS was calculated until the date of first relapse, death from any cause or the last follow-up for patients alive in CR. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood or BM (>5%) after CR. NRM was defined as death from any cause other than relapse. Acute GVHD was graded according to the modified Seattle Glucksberg criteria[14] and cGVHD according to the revised Seattle criteria[15]. Neutrophil engraftment was defined as first of 3 consecutive days with a neutrophil count of at least $0.5x10^9$/L.

MAC was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gray, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg or melphalan at doses >140 mg/m2. In addition,

regimens containing two alkylating agents were considered as MAC. All other regimens were defined as RIC.

Statistical analysis

Quantitative variables are described with median and range. Categorical variables are reported with counts and percent.

GRFS, LFS and OS were estimated by the Kaplan–Meier method. Cumulative incidence (CI) functions were used to estimate neutrophil engraftment, aGVHD, cGVHD, RI and NRM. Competing risks were death for RI, relapse for NRM, relapse or death for aGVHD and cGVHD. Univariate analyses were done using the log-rank test for GRFS, OS and LFS, and Gray's test for CI.

For univariate analysis, comparisons were made by using chi-squared tests for categorical and Mann-Whitney tests for continuous variables. Multivariate analyses were performed using the Cox proportional hazard model.

Stem cell source, diagnosis, disease status, age at transplant, transplant year, cytomegalovirus (CMV) serostatus (donor and recipient negative versus other combination), conditioning regimen and center experience were included in the final model.

The significance level was fixed at 0.05, and P values were two-sided. Statistical analyses were performed with the SPSS 22 (SPSS Inc./IBM, Armonk, NY, USA) and R 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

CENTER EFFECT (method ML)

Results

Patient and transplant characteristics

Table 1 summarizes the main characteristics. Four hundred fifty one patients were reported, 260 received BM as source of stem cell and 191, PB. The majority of the patients in both groups were transplanted for AML (73%) in CR1 (67%). The median age at transplantation was 45 (18-76) years.

Median follow up was longer for patients receiving BM (22.8 vs 18.3 months) and those patients were more likely transplanted with MAC (61% vs 49%, p=0.008). The combination of thiotepa, busulfan and fludarabine (Flu) (TBF) or FluCy and low dose total body irradiation (TBI) were the most common conditioning regimen used in MAC and RIC setting, respectively.

All patients received PT-Cy as GVHD prophylaxis, mainly in combination with calcineurin inhibitor and mycophenolate mofetil (MMF), according to the transplant center policy. The use of ATG use was not different for the 2 groups (5% vs 7%, p=0.41).

Median CD34+ was 2.8 x10^6/kg and 6.8 x10^6/kg for BM and PB, respectively p<0.001.

Neutrophil engraftment and GVHD

The CI of neutrophil engraftment was 92% and 95% for patients receiving BM and PB, respectively (p<0.001). The time to neutrophil engraftment was longer in the BM group (18 vs 17 days, p<0.001).

CI of day 100 grade II-IV acute GVHD and 1 year chronic GVHD were 28% and 35%.

In the univariate analysis (Table 2) patients transplanted with BM had a lower incidence of grade II-IV and grade III-IV acute GVHD (21% vs 38%, p=<0.01; and 4% vs 14%, p=<0.01, respectively) (Figure 1a). In multivariate analysis adjusted (Table 3), PB was independently associated with increased risk of grade II-IV acute GVHD (HR 2.1, 95%CI 1.46-3.0, p<10-4) and grade III-IV aGVHD (HR 3.8, 95%CI 1.7-8.2, p<0.001).

No difference in chronic GVHD (36% vs 32%, p=0.28) was observed in recipients of BM vs PB grafts (Figure 1b). Similarly, type of stem cell (PB vs BM) was not associated with cGVHD (HR 1.0, 95%CI 0.58-1.9, p=0.88) in the multivariate analysis (Table 3).

Relapse and NRM

At 2 years the CI of relapse was 25% with no difference according to the stem cell source (BM 26% vs PB 22%, p=0.38) (Figure 1c). CI of relapse was 22.4% for AML and 30.8% for ALL, p=0.04 and it was 22.2% and 29.6% for patients transplanted in CR1 and in CR2, p=0.08, respectively (Table 2).

Acute or chronic GVHD were not associated with relapse incidence in a time dependent fashion model (data not shown). Overall 2 years NRM was 23% with no difference for BM or PB recipients (23% vs 23%, p=0.61) (Table 2) (Figure 1d). Main causes of death were disease recurrence (BM 33%, PB 39%), infections (BM 39%, PB 33%) and GVHD (BM 14%, PB 17%).

In multivariate analysis (Table 3) the type of stem cell graft (PB vs BM) was not associated with relapse (HR 0.8, 95%CI 0.51-1.15, p=0.21), or NRM (HR 0.81, 95%CI 0.49-1.32, p=0.4). RIC regimen was the only factor associated with an increased risk of relapse (HR 1.62, 95%CI 1.07-2.44, p=0.02).

OS, LFS and GRFS

Overall OS, LFS and GRFS at 2 year were 55%, 51% and 44%, respectively.

According to stem cell source, OS was 55% vs 56% (p=0.57), LFS was 49% vs 54%, p=0.74 and GRFS was 44% and 43%, p=0.39, BM and PB, respectively (Figure 2a and 2b).

LFS was 53% for patients transplanted for AML and 47% for those with ALL (p=0.32), and it was 56% and 46% (p=0.004) for MAC vs RIC recipients, respectively. (Table 2)

In multivariate analysis (Table 3), the use of BM or PB was not associated with GRFS (HR 0.96, 95%CI 0.69-1.33, p=0.82), LFS (HR 0.74, 95%CI 0.52-1.04, p=0.08) and OS (HR 0.79, 95%CI 0.54-1.15, p=0.23). For LFS and OS, the use of RIC regimen was the only factor associated with higher risk of treatment failure (LFS: HR 1.40, 95%CI 1.01-1.93, p=0.04; OS: HR 1.5, 95%CI 1.07-2.14, p=0.02). Center effect, entered as a frailty variable in multivariate model was significant for NRM, LFS, GRFS, OS and cGVHD (Table 3).

Discussion

The number of transplants from an HLA partially matched related donor[16] is constantly increasing in the recent years due to the use of novel strategies without ex-vivo T-cell depletion. Non T depleted approaches are attractive because the treatment requires no expertise in graft manipulation and CD34+ cell selection, and allowed an important reduction of costs making the procedure affordable for the majority of transplant centers. In addition, familiar donors are easily available, the procedure may be organized fast, avoiding delay caused by the search of unrelated donor. The attractiveness of haplo-SCT should be verified by detailed analysis of results, as potential advantages may be counterbalanced by increased risk of immune-related complications. Despite short follow up several studies reported comparable outcomes after haploidentical SCT and HLA matched sibling and unrelated donors. [17-19]

The application of unmanipulated haploidentical transplants to adults with different hematological diseases, leads to investigate the feasibility of using different stem cell sources in this setting. The first reports using BM mainly in a non myeloablative setting with low dose TBI, were associated with low incidence of GVHD both acute and chronic, counterbalanced by an excess in disease recurrence[20]. This prompted some investigators to assess the use of PB in

this setting, facing the risk of severe GVHD.[11] With the aim to analyze the effect of the stem cell sources in patients with acute leukemia, we compared the outcomes of transplant with BM versus PB from haploidentical donor by using data reported to the ALWP-EBMT registry.

In our study, overall survival and LFS were not different using BM versus PB grafts, consistent with data of prospective and retrospective studies using MAC or RIC in sibling and unrelated donors [21,22] Engraftment of myeloid cells was higher with PB in comparison to BM grafts. This finding is in agreement with many previous reports indicating faster engraftment with PB versus BM grafts in different other transplant setting[1].

In the haploidentical setting, retrospective studies comparing the type of stem cells source using PT-Cy were published, showing no difference in the incidence of GVHD and survival.[12,23,24] These analyses included RIC transplants and patients with heterogenous myeloid and lymphoid malignancies.

Interestingly, an advantage in survival and progression free survival of PB over BM has been recently reported in 62 patients receiving a haploidentical transplant for advanced Hodgkin disease[25]. The biology of this disease and its sensitivity to the immunological effect mediated by the haploidentical cells, may in part explain this finding.

We observed significant differences in incidence of severe acute GVHD comparing PB and BM grafts in homogenous group of patients with AML. In accordance, BM with PT-Cy was reported to be associated with a low incidence of GVHD in different single centers reports[7,26]. The action of PT-Cy in preventing GVHD after BM graft has been nicely elucidated mediating selective in vivo destruction of alloreactive T cells, induction of tolerance and intra-thymic clonal delection of allo-reactive T lymphocytes[27].

One could argue that the lymphocyte count infused with the unmanipulated PB graft in the setting of fully haplotype mismatch could be responsible of an increase of acute GVHD, however one of the limitation of our registry based study is the lack of CD3+ cell number infused with the graft.

We did not find difference in chronic GVHD according to stem cell source. This finding is consistent with reports in the unrelated[2] and haploidentical[12] setting using RIC regimens.

Of note, in our study the difference in acute GVHD was not reflected in an excess of non relapse mortality, neither in GRFS, LFS and OS. This may also be due to the substantial

improvements in supportive care after allogeneic transplant over the years, allowing better survival and reduction of treatment related toxicities.

The type of conditioning regimen was an independent factor associated with relapse and LFS and OS, with RIC associated with treatment failure. RIC regimens are known to be more at risk of increase of disease relapse. Large registry studies observed that the use of RIC regimen was associated with a higher risk of relapse, but also a lower incidence of NRM translating to similar OS and LFS[28,29]. More recently, the BMT-CTN performed a randomized study comparing RIC versus MAC in adults up to 65 years with myeloid malignancies [30] confirming higher relapse rate and lower NRM using RIC and higher LFS compared with MAC.

Others did not detect difference in outcomes with RIC versus MAC in unmanipulated haploidentical transplants, however this series included a quite heterogeneous population of patients with different disease status and several platforms of GVHD prophylaxis[31].

We are aware that in our study there may be unmeasured factors that have not been considered, and this is a limitation when conducting retrospective studies. With the available data, our study indicates that in patients with acute leukemia in first or second CR receiving haploidentical transplant with PT-Cy, the use of PB significantly increases the risk of acute GVHD, whereas survival outcomes were comparable. Importantly with a follow up of 2 years, cGVHD, which is a major contributor to long term morbidity and mortality, is similar using PB or BM grafts.

The ultimate choice of graft source depends on the design of the full transplant package based on transplant center experience. Our results suggest a prospective evaluation of PB versus BM comparative trial in PT-Cy haploidentical transplant that hopefully will lead to establish a standard in the field.

Authorship and Disclosures: AR, ML, AN designed the study, AR, ML performed the statistical analysis, AR wrote the manuscript, AB, ZG, YC, DB, BB, GI, JT, JD, LC, FC, MM provided cases for the study. All authors edited and approved the manuscript. The authors have no conflict of interest to disclose.

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Participating center:

Figure legend

Figure 1. 1a. aGVHD III-IV; 1b. cGVHD; 1c. RI; and 1d. NRM for BM and PB recipients

Figure 2. 2a. OS; 2b. LFS for BM and PB recipients

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Figure 1a

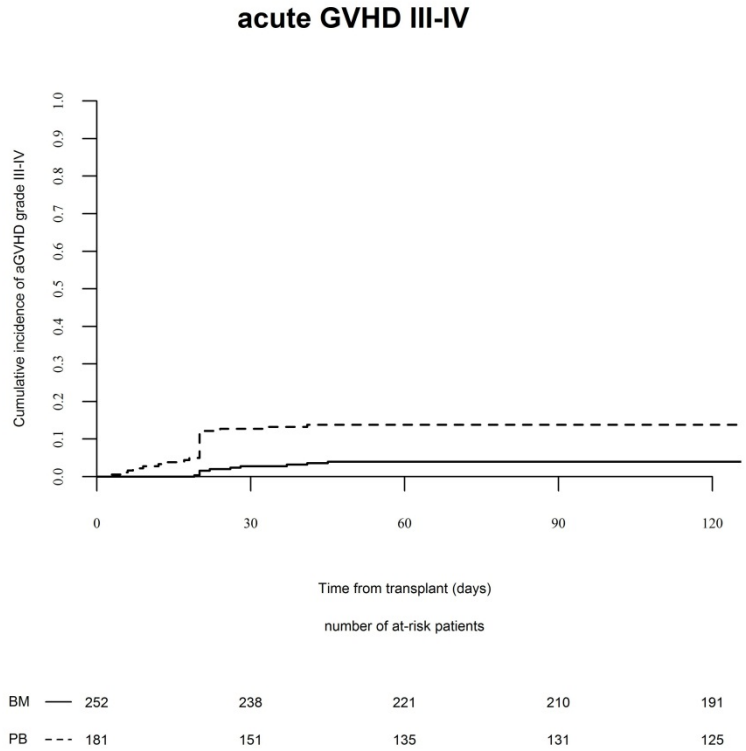
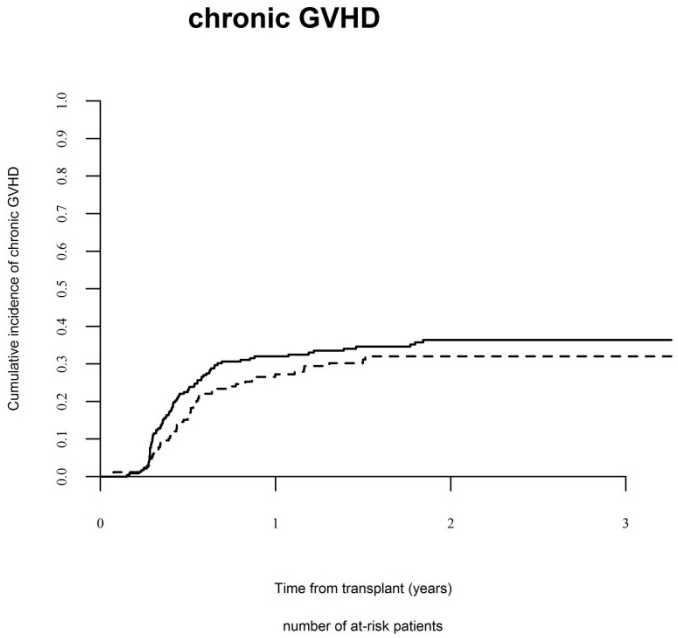
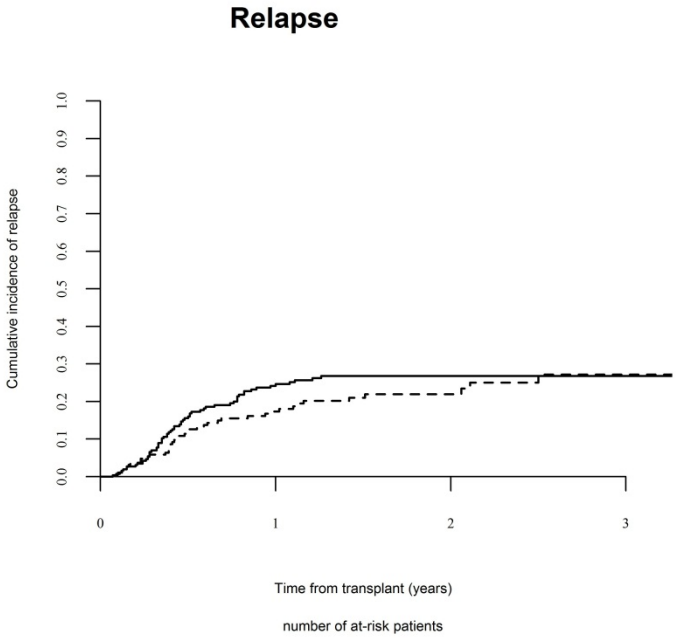

acute GVHD III-IV
Cumulative incidence of aGVHD grade III-IV
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
30
60
90
120
Time from transplant (days)
number of at-risk patients
BM 252 238 221 210 191
PB 181 151 135 131 125

Figure 1b



BM	238	74	38	17
PB	171	60	19	5

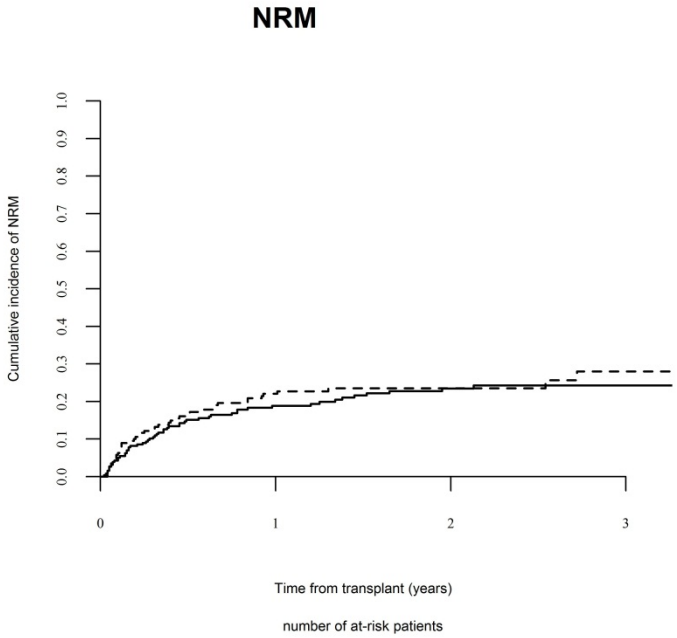
Figure 1c



number of at-risk patients

BM	260	118	71	38
PB	191	96	39	12

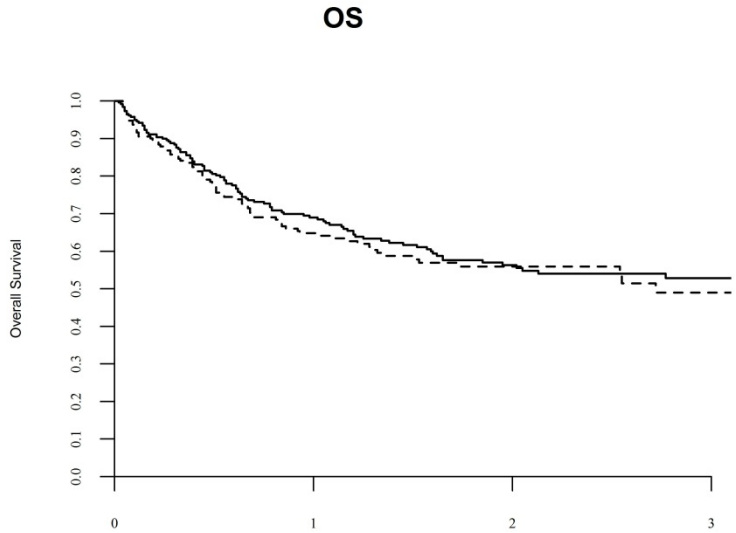
Figure 1d



number of at-risk patients

BM	260	118	71	38
PB	191	96	39	12

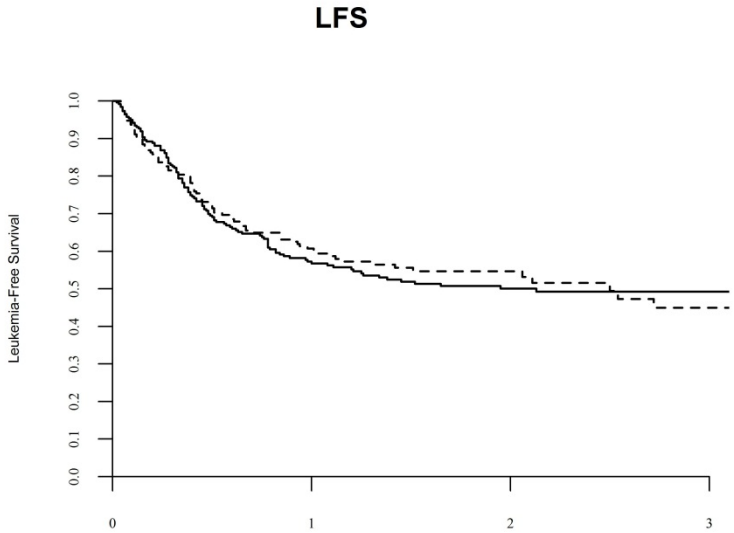
Figure 2a



number of at-risk patients

BM	——	260	144	79	41
PB	- - - -	191	102	41	13

Figure 2b



number of at-risk patients

BM	——	260	118	71	38
PB	- - - -	191	96	39	12

Table 1. Patients and transplant characteristics

	BM	PB	p
N	260	191	
Follow-up median (range)	22.8 (2.4-62.4)	18.3 (1.6-50.5)	0.42
Patient age median (range)	46.5 (18.4-74.8)	44.4(18.2-74.9)	0.88
Time from diag to Tx median (range)	7.7 (2-100.3)	8.1 (2-237.9)	0.56
Year of Tx median (range)	2013 (2010-2014)	2013 (2010-2014)	0.15
AML	195 (75%)	136 (71%)	0.36
ALL	65 (25%)	55 (29%)	
CR1	174 (67%)	131 (69%)	0.70
CR2	86 (33%)	60 (31%)	
de novo AL	225 (87%)	155 (81%)	0.12
sec. AL	35 (13%)	36 (19%)	
CMV D-/R-	25 (10%)	18 (9%)	0.04
CMV D+/R+	153 (60%)	132 (70%)	
MAC	159 (61%)	93 (49%)	**0.008**
RIC	101 (39%)	98 (51%)	
No ATG	247 (95%)	178 (93%)	0.41
ATG	13 (5%)	13 (7%)	

Table 2. Univariate analysis

	Relapse	NRM	LFS	OS	GRFS	aGVHD II-IV	aGVHD III-IV	cGVHD	ext. cGVHD
BM	26.8%[21.2-32.6]	23.5%[18.1-29.3]	49.4%[42.7-56.1]	55.5%[48.7-62.3]	44%[37.5-50.5]	21.6%[16.7-26.9]	4%[2-6.9]	36.4%[30-42.8]	12.3%[8.3-17.1]
PB	21.9%[15.9-28.6]	23.5%[17.5-30]	54.4%[46.8-62.1]	55.6%[47.8-63.5]	43.2%[35.7-50.7]	38.3%[31.2-45.3]	13.8%[9.3-19.3]	32.1%[24.8-39.6]	10.3%[6.1-15.7]
P value	0.38	0.60	0.74	0.57	0.39	0.0004	0.0001	0.28	0.48
Age<45y	28.2%[22-34.6]	22%[16.5-28]	49.4%[42.3-56.5]	56.9%[49.6-64.1]	39.2%[32.3-46]	29.8%[23.8-36]	10.7%[7-15.2]	33.7%[26.9-40.6]	11.4%[7.3-16.6]
Age>=45y	21.1%[15.8-27]	25.3%[19.3-31.7]	53.5%[46.3-60.7]	54%[46.6-61.4]	48%[41-55]	27.3%[21.5-33.4]	5.5%[3-9.1]	35.6%[28.8-42.5]	11.4%[7.4-16.4]
P value	0.13	0.40	0.54	0.54	0.10	0.48	0.04	0.68	0.99
Interval diag-Haplo <8 mo	22.7%[17.1-28.7]	21%[15.5-27.1]	55.9%[48.8-63.1]	59.5%[52.2-66.8]	47.7%[40.7-54.6]	26.5%[20.8-32.6]	8.8%[5.5-13.1]	39.7%[32.6-46.7]	12.6%[8.3-17.8]
Interval diag-Haplo >=8 mo	26.6%[20.6-32.9]	26.3%[20.3-32.6]	47%[39.9-54.1]	51.5%[44.2-58.8]	39.7%[32.9-46.6]	30.6%[24.5-36.8]	7.3%[4.4-11.3]	29.5%[23.1-36.3]	10.2%[6.4-15.1]
P value	0.44	0.27	0.10	0.07	0.17	0.50	0.56	0.02	0.45
year<2013	31.7%[24.1-39.6]	19.7%[13.5-26.8]	48.1%[39.7-56.5]	53.7%[45.3-62.1]	38.8%[30.6-47]	23.8%[17.1-31.2]	7.2%[3.7-12.3]	38.6%[30.3-46.7]	14.8%[9.4-21.4]
year>=2013	20.7%[16-25.8]	25.8%[20.5-31.4]	53.4%[47.1-59.7]	56.8%[50.3-63.3]	46.4%[40.3-52.5]	30.8%[25.6-36.2]	8.5%[5.7-12.1]	32.7%[26.7-38.8]	9.6%[6.2-13.8]
P value	0.02	0.16	0.43	0.60	0.28	0.15	0.65	0.15	0.11
AML	22.4%[17.8-27.4]	24.4%[19.6-29.5]	53%[47.2-58.9]	56%[50-62]	44.7%[38.9-50.4]	26%[21.3-31]	7.6%[5-10.9]	33%[27.5-38.6]	11.6%[8.2-15.8]
ALL	30.8%[22.2-39.9]	21.5%[14.1-29.9]	47.1%[37.2-57]	53.8%[43.7-64]	40.6%[31.2-50]	35.5%[26.9-44.3]	9.5%[5-15.7]	39.3%[29.5-49]	10.9%[5.7-17.9]
P value	0.04	0.38	0.31	0.79	0.23	0.04	0.50	0.22	0.96
CR1	22.2%[17.4-27.4]	24.4%[19.3-29.8]	53.1%[46.9-59.4]	57.7%[51.4-64]	46.5%[40.6-52.5]	24.7%[19.9-29.7]	8.9%[6-12.5]	33.8%[27.9-39.7]	10.2%[6.9-14.4]
CR2	29.6%[22-37.5]	22.2%[15.5-29.7]	48%[39.3-56.6]	51.1%[42.1-60.1]	37.9%[29.5-46.3]	36.7%[28.7-44.7]	6.4%[3.2-11.3]	36.2%[27.8-44.6]	13.6%[8.3-20.3]
P value	0.08	0.50	0.36	0.33	0.32	0.02	0.38	0.75	0.38
de novo AL	25%[20.4-29.7]	23.6%[19.1-28.4]	51.2%[45.7-56.7]	55.7%[50-61.4]	43%[37.7-48.4]	29.5%[24.9-34.3]	8.8%[6.2-12]	36.2%[30.9-41.6]	12.4%[9-16.4]
sec. AL	23%[13.5-33.9]	23.9%[14.4-34.7]	52.8%[40.5-65]	53.9%[41.3-66.6]	47.1%[34.9-59.3]	23.5%[14.2-34.2]	4.4%[1.2-11.3]	26.6%[15.9-38.5]	6.3%[2-14.3]
P value	0.79	0.38	0.64	0.20	0.69	0.35	0.22	0.11	0.18
No F->M	24.1%[19.4-29.1]	23.4%[18.8-28.4]	52.2%[46.5-58]	56%[50.1-61.9]	45.7%[40.1-51.4]	28.6%[23.8-33.6]	8.5%[5.8-11.8]	31.9%[26.5-37.4]	9.5%[6.4-13.2]
F->M	26.2%[17.9-35.4]	24.4%[16-33.7]	49.1%[38.7-59.5]	53.6%[42.9-64.4]	37.4%[27.8-47.1]	28.3%[19.9-37.3]	6.8%[3-12.8]	42.9%[32.3-53]	17.4%[10.4-25.9]
P value	0.84	0.76	0.78	0.96	0.26	0.97	0.60	0.10	0.04

CMV D-/R-	28%[14.9-42.6]	34.3%[18.8-50.5]	37.7%[21.3-54.1]	38%[20.5-55.5]	30%[15.4-44.6]	31%[17.2-45.9]	7.7%[1.9-18.8]	26.4%[13.4-41.3]	13.5%[4.8-26.7]
CMV D+/R-	20.6%[7.9-37.4]	19.6%[7.7-35.5]	59.8%[41.7-77.8]	65.9%[48.5-83.3]	52.7%[35-70.3]	29%[14.3-45.6]	6.5%[1.1-18.9]	39.6%[21.3-57.5]	14.3%[4.3-29.9]
CMV D-/R+	32.7%[22.1-43.6]	14.2%[7.1-23.5]	52.7%[40.9-64.5]	55.1%[43-67.2]	48%[36.4-59.7]	14.3%[7.5-23.1]	3.8%[1-9.9]	38.1%[25.9-50.3]	7.2%[2.6-15]
CMV D+/R+	22.8%[17.8-28.2]	25%[19.8-30.4]	52%[45.6-58.3]	56.9%[50.5-63.4]	43.1%[36.9-49.3]	32.9%[27.3-38.5]	9.8%[6.7-13.7]	33.5%[27.5-39.7]	11.6%[7.8-16.1]
P value	0.36	0.11	0.48	0.57	0.35	0.01	0.38	0.65	0.64
MAC	22.8%[17.4-28.6]	21.3%[16.1-27.1]	55.7%[48.8-62.5]	63.8%[57.1-70.5]	45%[38.4-51.6]	29.7%[24.1-35.5]	9.9%[6.5-14]	37.4%[30.7-44.2]	13.5%[9.2-18.6]
RIC	27%[20.7-33.6]	26.4%[20.2-33]	46.3%[38.9-53.7]	45.1%[37.3-52.9]	41.9%[34.7-49.2]	27.1%[20.9-33.6]	5.8%[3.1-9.8]	31.4%[24.5-38.5]	8.8%[5.1-13.7]
P value	0.12	0.10	0.004	0.0002	0.25	0.43	0.11	0.48	0.17
noATG	25.1%[20.8-29.5]	23%[18.8-27.4]	51.7%[46.5-56.9]	55.9%[50.5-61.2]	44.6%[39.5-49.6]	28.4%[24.1-32.9]	8.4%[5.9-11.3]	33.7%[28.8-38.7]	10.7%[7.8-14.3]
ATG	18%[5.2-37]	32.2%[14.9-51]	49.7%[29.2-70.3]	48.7%[25.8-71.5]	30.5%[12-49]	30.8%[14.3-49]	3.8%[0.3-16.8]	NA%[NA-NA]	21.3%[7.4-39.8]
P value	0.30	0.13	0.84	0.45	0.52	0.76	0.42	0.27	0.11

Table 3. Multivariate analysis

		HR	95%CI	P
aGVHD II-IV	**PB vs BM**	**2.09**	**1.45- 3.01**	**0.0007**
	age per 10 years	1.03	0.91 - 1.18	0.57
	Year of Tx	**1.23**	**1.02 - 1.47**	**0.02**
	ALL vs AML	**1.58**	**1.06 - 2.35**	**0.02**
	CR2 vs CR1	**1.71**	**1.17 - 2.49**	**0.005**
	CMV D-/R- vs other	1.00	0.54 - 1.84	0.98
	RIC vs MAC	0.79	0.54 - 1.16	0.23
	Centre (frailty)			0.92
cGVHD	PB vs BM	1.04	0.57 - 1.90	0.87
	age per 10 years	0.98	0.84- 1.14	0.84
	Year of Tx	0.90	0.75 - 1.08	0.26
	ALL vs AML	1.21	0.79 - 1.87	0.36
	CR2 vs CR1	1.01	0.67 - 1.50	0.95
	CMV D-/R- vs other	0.83	0.40 - 1.71	0.62
	RIC vs MAC	1.40	0.88- 2.24	0.14
	Centre (frailty)			**0.0003**
RELAPSE	PB vs BM	0.76	0.51- 1.15	0.21
	age per 10 years	0.93	0.81- 1.08	0.38
	Year of Tx	0.91	0.76- 1.09	0.32
	ALL vs AML	1.50	0.97- 2.31	0.06
	CR2 vs CR1	1.29	0.85- 1.94	0.22
	CMV D-/R- vs other	1.14	0.60- 2.17	0.68
	RIC vs MAC	**1.61**	**1.06- 2.44**	**0.02**
	Centre (frailty)			0.31
NRM	PB vs BM	0.80	0.49- 1.32	0.40
	age per 10 years	1.14	0.98- 1.34	0.08
	Year of Tx	1.04	0.85- 1.28	0.66
	ALL vs AML	1.02	0.61- 1.70	0.93
	CR2 vs CR1	0.81	0.51- 1.29	0.39
	CMV D-/R- vs other	1.57	0.82- 2.99	0.17
	RIC vs MAC	1.25	0.79- 1.99	0.33
	Centre (frailty)			**0.04**

LFS	PB vs BM	0.73	0.51- 1.04	0.08
	age per 10 years	1.03	0.93- 1.15	0.53
	Year of Tx	0.95	0.83- 1.09	0.54
	ALL vs AML	1.28	0.92- 1.80	0.14
	CR2 vs CR1	1.03	0.75- 1.40	0.84
	CMV D-/R- vs other	1.29	0.81- 2.05	0.27
	RIC vs MAC	1.39	1.01- 1.93	**0.04**
	Centre (frailty)			0.06
OS	PB vs BM	0.79	0.54- 1.15	0.23
	age per 10 years	1.11	0.99 - 1.24	0.06
	Year of Tx	0.95	0.82- 1.10	0.54
	ALL vs AML	1.24	0.86- 1.79	0.24
	CR2 vs CR1	1.07	0.77-1.49	0.65
	CMV D-/R- vs other	1.21	0.74- 1.98	0.43
	RIC vs MAC	1.51	1.06 - 2.13	**0.01**
	Centre (frailty)			**0.01**
GRFS	PB vs BM	0.96	0.69 - 1.33	0.82
	age per 10 years	1.01	0.92 - 1.12	0.72
	Year of Tx	0.95	0.84 - 1.08	0.44
	ALL vs AML	1.23	0.90 - 1.67	0.18
	CR2 vs CR1	1.03	0.78 - 1.37	0.81
	CMV D-/R- vs other	1.36	0.89 - 2.09	0.15
	RIC vs MAC	1.05	0.78 - 1.42	0.72
	Centre (frailty)			0.05