



## Predictive Factors for Outcome of First Allogeneic Transplant for Elderly Patients With Acute Lymphoblastic Leukemia

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## AlloHCT in elderly ALL patients

### **Predictive factors for outcome of first allogeneic transplant for elderly patients with acute lymphoblastic leukemia**

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**MICRO ABSTRACT**

Acute lymphoblastic leukemia (ALL) in elderly patients is challenging, and while allogeneic stem cell transplantation (alloHCT) has established benefits in younger candidates, its use in the elderly can be difficult. We identified 84 ALL patients 70 years or older in the EBMT registry that underwent alloHCT. Our results demonstrate favorable outcome especially in those achieving first complete remission with >50% 2-year OS. AlloHCT appears feasible in select elderly ALL patients.

**CLINICAL PRACTICE POINTS**

- What is already known about this subject?

Acute lymphoblastic leukemia (ALL) has dismal outcome in elderly patients, and while allogeneic stem cell transplantation (alloHCT) has established benefits in younger candidates, its use in the elderly can be difficult.

- What are the new findings?

AlloHCT appears feasibly in elderly patients and our results demonstrate favorable outcome especially in those achieving first complete remission with >50% 2-year OS.

- How might it impact on clinical practice in the foreseeable future?

We believe our results can help shift the paradigm of alloHCT usage in elderly patients as it appears to be a valid option especially in carefully selected candidates.

**ABSTRACT**

The treatment of acute lymphoblastic leukemia (ALL) in patients older than 70 is extremely challenging with dismal outcome. Allogeneic stem cell transplantation (alloHCT) has seen many advancements in the last decades showing benefits in younger ALL patients, but this treatment modality is decreasingly used with increasing age due to high treatment-related mortality. We identified 84 ALL patients 70-84 years old allografted in 2002-2019 from a matched related (23%), unrelated (58%), haploidentical (17%) or cord blood (2%) donor at EBMT participating centers with a median follow-up of 23 months. The 2-year relapse incidence (RI) and non-relapse mortality (NRM) were 37% and 28%, respectively, and 2-year leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) were 35%, 39% and 23%, respectively. The strongest predictor of outcome was disease status at transplant whereby patients in first complete remission (CR1) had >50% 2-year OS, reflected in multivariate analysis (MVA) with significant improvement in RI, LFS and GRFS (HR 0.23, 0.49 and 0.54, respectively). Furthermore, karnofsky score  $\geq 90$  reflective of good functional status positively influenced NRM in both univariate and MVA (HR 0.37), and interestingly, donor CMV positivity appeared to negatively affect RI, LFS and OS in univariate analysis and RI in MVA (HR 2.87). Our data suggest that alloHCT is an option for elderly ALL patients, particularly those carefully selected and

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transplanted in CR1 especially if failed or without access to novel non-chemotherapy-based approaches.

### **KEYWORDS**

Acute lymphoblastic leukemia; allogeneic stem cell transplantation; elderly patients; complete remission; haploidentical transplantation; graft-versus-host disease.

### **ABBREVIATIONS**

- Acute lymphoblastic leukemia (ALL)
- Overall survival (OS)
- Allogeneic stem-cell transplantation (alloHCT)
- Total body irradiation (TBI)
- Reduced-intensity conditioning (RIC)
- Acute Leukemia Working Party (ALWP)
- European Society for Blood and Marrow Transplantation (EBMT)
- Karnofsky performance status (KPS)
- Graft-versus-host disease (GVHD)
- Cytomegalovirus (CMV)
- Myeloablative conditioning (MAC)
- Leukemia free survival (LFS)
- Non-relapse mortality (NRM)

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- 107 - Relapse incidence (RI)
- 108 - GVHD-free, relapse-free survival (GRFS)
- 109 - Complete remission (CR)
- 110 - Hazard ratio (HR)
- 111 - Confidence interval (CI)
- 112 - Philadelphia chromosome (Ph)
- 113 - Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI)
- 114 - T cell depletion (TCD)
- 115 - Chimeric antigen receptor (CAR)
- 116 - Pegylated-asparaginase (PEG-ASP)
- 117 - Tyrosine kinase inhibitor (TKI)
- 118 - Minimal residual disease (MRD)
- 119 - Acute myeloid leukemia (AML)
- 120

## INTRODUCTION

The management of acute lymphoblastic leukemia (ALL) in elderly patients is challenging with a generally dismal outcome. In fact, while patients above the age of 55 only constitute around a fifth of diagnosed ALL, they account for over half of ALL-related deaths.<sup>1</sup> This striking discrepancy is explained by age-related increased comorbidities and higher-risk genetic alterations leading to lower remission rates, higher relapse rates, and poor overall survival (OS). Patients often do not respond well to chemotherapy, and even those achieving remission have <25% 5-year survival.<sup>2</sup> While the benefits of allogeneic stem-cell transplantation (alloHCT) in younger ALL patients have been well established, with a long term survival advantage exceeding 4 fold in certain patients,<sup>3-7</sup> its indication for elderly patients is controversial and rarely made due to its concomitant high treatment-related mortality,<sup>8</sup> and older patients are often excluded from investigational trials. Furthermore, many of the alloHCT for ALL are based on myeloablative total body irradiation (TBI) which cannot be delivered to elderly patients due to high toxicity.<sup>9-15</sup> Many advancements in reduced-intensity conditioning (RIC) have been made however, which is proving to be a promising option for selected patients and increasing study eligibility.<sup>15,16</sup> Clinical trials with alloHCT in elderly patients remain extremely rare, and results from both prospective and retrospective studies have so far yielded conflicting results with little evidence for benefit of transplant in such patients.<sup>17,18</sup> This missing gap in the literature drove us to



conduct this retrospective analysis using the European Society for Blood and Marrow Transplantation (EBMT) registry, which we believe will provide better understanding of alloHCT outcome and whether this modality is feasible in this population.

## **MATERIALS AND METHODS**

### *Study Design and Data Collection*

This was a retrospective, registry-based, multicenter analysis. Data were provided and approved by the Acute Leukemia Working Party (ALWP) of the EBMT.<sup>19</sup> The EBMT is a voluntary collaborating working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-up once a year, with regularly performed audits to determine the accuracy of the data. Since the 1<sup>st</sup> of January 2003, all transplantation centers have been required to obtain written informed consent prior to data registration with the EBMT, as per the guidelines of the Declaration of Helsinki of 1975.

Eligibility criteria for this analysis included elderly patients (aged  $\geq 70$  years) with ALL who received a first alloHCT between 2000 and 2019 from an HLA-matched related, unrelated, haploidentical or cord blood donor with bone marrow, peripheral blood or cord blood stem cells. Variables collected included recipient

and donor age and gender, date of diagnosis, disease status and Karnofsky performance status (KPS) score at the time of transplant. Transplant-related factors included date, conditioning regimen and graft-versus-host disease (GVHD) prophylaxis, *in vivo* T-cell depletion, donor type, and patient and donor cytomegalovirus (CMV) status.

### *Definitions*

Myeloablative conditioning (MAC) was defined as a regimen containing either TBI with a dose  $\geq 8$  Gy, a total dose of oral busulfan (Bu)  $> 8$  mg/kg, or a total dose of intravenous Bu  $> 6.4$  mg/kg. All other regimens were defined as RIC.<sup>20</sup> Diagnosis and grading of acute<sup>21</sup> and chronic GVHD<sup>22</sup> were performed by transplant centers using standard criteria. High-resolution HLA allele typing at loci A, B, C, DRB1 and DQ was retrieved from the EBMT registry for both the patient and the donor.

### *Endpoints*

Endpoints included leukemia free survival (LFS), OS, non-relapse mortality (NRM), relapse incidence (RI), acute and chronic GVHD, and GVHD-free, relapse-free survival (GRFS), with all outcomes measured from the time of alloHCT. LFS was defined as survival without leukemia relapse or progression, with patients censored at the time of last contact. OS was defined as the time until death from any cause. NRM was defined as being alive until death with no previous leukemia relapse. GRFS was defined as being alive with neither grade III-IV acute GVHD,

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extensive chronic GVHD, nor relapse.<sup>23</sup> Surviving patients were censored at the time of last contact.

### *Statistical analysis*

The Kaplan-Meier method was used to calculate the probabilities of OS and LFS. Cumulative incidence functions were used to estimate RI and NRM in a competing risk setting. Death and relapse were considered as competing events for acute and chronic GVHD.

Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS, and LFS. A Cox proportional hazards model was used for multivariate regression, including status of the disease at HSCT (first complete remission [CR1] vs other), donor type (MSD vs other), year of HSCT and factors associated with the outcome in univariate. Results were expressed as hazard ratio (HR) with a 95% confidence interval (CI). All tests were two sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R version 3.4.0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

## **RESULTS**

*Patient and Transplantation Characteristics*

Eighty-four patients (43% female; median age 72 years; range 70-84) met the eligibility criteria and were included in this study (Tables 1 & 2) with a median follow-up for alive patients of 23 months (IQR 6-46). More than half (53%) of the patients were in CR1, 26% were in second or subsequent remission (CR2+), and 21% had advanced disease. Thirteen % had T-cell acute lymphoblastic leukaemia (T-ALL), 35% were Philadelphia chromosome positive, 21% were Philadelphia chromosome (Ph) negative, and 31% had B-cell acute lymphoblastic leukemia (B-ALL) with unknown Ph status. The KPS score was  $\geq 90$  in 59% of the patients and the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was 1-2, and  $\geq 3$  in 11% and 17% of patients, respectively. Conditioning was MAC in 22.6% of the patients (Supplementary Table 1) and 40.5% received TBI. *In vivo* T cell depletion (TCD) was used in 55% of patients. Sixty-eight % of the patients and 57% of the donors were CMV positive. Sixteen percent of patients were males who received a graft from a female donor. Patients were allografted from a matched related (23%), matched unrelated (58%), haploidentical (17%) or cord blood donor (2%).

*Transplant outcomes*

Median time from diagnosis to alloHCT was 8.8 months (IQR 5.7-16.3). Day +180 acute GVHD grades II-IV and III-IV were encountered in 30% and 10% of patients,

respectively, whereas the 2-year cumulative incidence of chronic and extensive GVHD were 34% and 23%, respectively. The 2-year RI was 37% and NRM 28%. The 2-year LFS, OS and GRFS were 35%, 39% and 23%, respectively. (Tables 3 & 4) The main causes of death of the 46 deceased patients were primary disease (45%), infections (29%) and GVHD (10%) (Table 5).

In the univariate analysis (Tables 3 & 4), patient age, ALL subtype, conditioning intensity, TBI use, patient and donor gender, female to male donor, and *in vivo* TCD did not affect any of the transplant outcomes. On the other hand, at least one outcome was affected by the status at transplant, donor type, KPS score and HCT-CI, year of transplant, and patient and donor CMV serology. In fact, patients in CR1 had a significantly better 2-year outcomes compared to CR2+ and advanced disease with relapse rates of 14% versus 54% and 64% respectively ( $p=0.001$ ), LFS of 52% versus 21% and 18% respectively ( $p=0.009$ ), OS of 53% versus 33% and 21% respectively ( $p=0.029$ ), and GRFS of 36% versus 8% and 13% respectively ( $p=0.01$ ). (Table 3) (Figure 1). Patients with a KPS score  $\geq 90$  had a significantly lower NRM (17%) compared to 44% in those with a KPS  $< 90$  ( $p=0.016$ ), and those transplanted from CMV positive donors had a higher RI of 50% versus 21% in CMV negative donors ( $p=0.007$ ), and worse LFS (23% versus 49%;  $p=0.012$ ) and OS (25% versus 55%;  $p=0.024$ ) (Table 3). On the other hand, patients undergoing haploidentical transplants and those with HCT-CI scores  $\geq 3$  had significantly higher rates of day +180 grade III-IV acute GVHD (29%  $p=0.04$  and 36%  $p=0.015$  respectively). Patients transplanted before 2015 (median) had lower rates of day +180 grade II-IV acute

GVHD (14% versus 41%;  $p=0.016$ ) and 2-year chronic GVHD (13% versus 46%;  $p=0.018$ ), whereas patients with a positive CMV serology had lower rates of chronic (23% versus 55%;  $p=0.007$ ) and extensive chronic GVHD (11% versus 57%;  $p=0.001$ ) (Table 4).

In multivariate analysis (Table 6), CR1 was significantly associated with improved RI, LFS and GRFS with HR of 0.23 ( $p = 0.007$ ), 0.49 ( $p = 0.034$ ) and 0.54 ( $p = 0.027$ ) respectively. KPS above 90 was significant for improved NRM with a HR of 0.37 ( $p = 0.025$ ), and donor CMV positivity negatively affected RI with HR of 2.87 ( $p = 0.039$ ) but was no longer a predictor of LFS (HR 1.86;  $p = 0.062$ ) and OS (HR 1.96;  $p = 0.057$ ).

## DISCUSSION

In this study we evaluated the predictive factors for post-transplant outcome in elderly ALL patients above the age of 70 years using 84 patients from the EBMT registry. We found that RI, LFS, OS and GRFS were significantly better in patients transplanted after achieving CR1, and that RI (and possibly LFS and OS) were significantly worse if donors were CMV positive. A KPS score  $\geq 90$  at transplant was associated with better NRM but gave no overall survival benefit. These results may help guide treatment choice for this particularly challenging population.

The main challenges when treating elderly ALL patients are centered around the lack of options and effective treatment strategies. In fact, conventional

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chemotherapy has so far yielded suboptimal results in this population, and while younger counterparts are often offered more intensive therapies such as alloHCT and chimeric antigen receptor (CAR) T-cells, the more elderly are often left behind, as it can be difficult selecting those eligible and deciding on whether to use full-intensity regimens such as MAC and TBI.

Ph-negative ALL is drug-resistant by nature, and elderly patients often require reduction of key administered drugs throughout the course of therapy which reflects in poor outcome using conventional chemotherapy alone.<sup>9,11,12,24,25</sup>

Conversely, the proportion of Ph-positive ALL increases with increasing age, historically considered high-risk disease, the introduction of tyrosine kinase inhibitors (TKIs) led to better CR rates and lower induction mortality.<sup>26,27</sup> This has yet to reflect on long-term survival, as 5-year OS remains around 14% for patients older than 60 years receiving imatinib with full intensity regimens.<sup>28</sup>

High subsequent relapse rates could be overcome with the use of second and third generation TKIs owing to their higher potency.<sup>29-34</sup>

AlloHCT is considered a standard of care for high-risk ALL patients and offered as consolidation for all fit candidates when suitable donors are available. Elderly patients can be particularly challenging as they often present with high-risk disease and often lack the required fitness to undergo such intensive therapy.

Studies investigating alloHCT in older patients have reported a 3-year OS of around 40% with NRM from matched donors of approximately 25%.<sup>15,35</sup> While prospective randomized trials have yet to establish a definitive answer, our data

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suggest that alloHCT is feasible in patients above 70 years of age, with almost 40% surviving beyond 2 years, especially if transplanted in CR1 where survival exceeds 50%. It is important to note that although a bad KPS score was associated with higher NRM, there was no impact on LFS, OS, nor GRFS, likely because of small numbers.

An important aspect and possible setback when considering alloHCT is donor availability and optimal selection. Physicians are often torn between proceeding with the first available donor or waiting for a more optimally matched one to maximize outcome. Matched related donors are traditionally favored, but advancements in haploidentical alloHCT has significantly improved outcomes for candidates lacking such donors,<sup>36-38</sup> a challenge particularly faced with elderly patients. There are data that even suggest better outcomes compared to matched sibling donor for minimal residual disease (MRD)-positive disease.<sup>39</sup> It has been also recently published that all donor choices provide comparable results in certain ALL patients,<sup>37,40,41</sup> which appears to apply to elderly patients as donor type had no measurable impact on outcome suggesting that the first available donor should be used regardless of compatibility.

While data from alloHCT in elderly ALL patients remain scarce, results can also be extrapolated from elderly acute myeloid leukemia (AML) patients. Recently published data from the ALWP comparing outcomes between 713 patients  $\geq 70$  years and 16,161 patients age 50 to 69 years with AML who underwent alloHCT between 2004 and 2014 have shown worse outcomes in elderly patients except



those with active disease.<sup>42</sup> In fact, survival at 2 years was 38% (95% CI 34%-42%) in elderly group compared to 50% (95% CI 49%-50%) in the younger patients ( $p < 0.001$ ). In patients with active disease, corresponding percentages were 35% (95% CI 29%-41%) in the elderly and 33% (95% CI 31%-34%) in younger patients ( $p = 0.36$ ).

There is mounting interest for earlier use of novel agents such as inotuzumab and blinatumomab in ALL treatment given their impressive activity and tolerability which has also been reflected in the elderly population. Inotuzumab in combination with low-dose cyclophosphamide, dexamethasone and methotrexate in newly diagnosed elderly Ph-negative ALL patients (median age 68 years) was shown to be safe and highly efficacious with CR rates reaching 98%.<sup>43</sup> This was reflected by a 3-year OS of 56%, far superior to standard chemotherapy. Blinatumomab is currently being investigated both as frontline and relapse therapy in combination with the POMP regimen (mercaptopurine, vincristine, methotrexate, and prednisone) (ClinicalTrials.gov identifier: NCT02143414), dasatinib and corticosteroids (ClinicalTrials.gov identifier: NCT02143414, NCT02744768), and tyrosine kinase inhibitors in Ph-positive patients (ClinicalTrials.gov identifier: NCT03263572). Patients with T-ALL however, lack the availability of such novel drugs and currently remain with an unmet treatment need. A sequential-based conditioning for these patients can therefore be an option, especially in the relapsed/refractory RR setting.<sup>44</sup>

CAR T-cells are also emerging for the treatment of ALL especially in the RR setting. The CD19-directed CAR T Isagenlecleucel yielded impressive results with 80% CR rates in heavily pretreated ALL mostly in pediatric patients.<sup>45</sup> This led to its approval as salvage therapy by the FDA for young ( $\leq 25$  years) fit RR-ALL patients.<sup>46</sup> The ZUMA-3 study is a phase I trial investigating the use of KTE-X19, an autologous anti-CD19 CAR T in RR adult ALL patients.<sup>47</sup> Recently published interim analysis of 45 patients ranging from 18 to 77 years of age over 16 months median follow-up showed acceptable safety and encouraging efficacy with up to 84% of patients achieving CR or CR with incomplete bone marrow recovery and a median survival of 15 months. Phase II results are still awaited.

#### **LIMITATIONS**

Many challenges were faced during the design and data analysis of this study, and results should be interpreted with caution. Firstly, this study was limited by its retrospective registry-based nature, and by the inclusion of only transplant-eligible patients. The authors acknowledge that there is a probable selection bias whereby only relatively fit elderly patients were deemed eligible for transplant, not necessarily reflective of all elderly ALL patients above 70. Similarly, the patient group was treated over an 18-year period which accounts for a relatively narrow subgroup of all ALL transplants, again putting into question the data generalizability. While multivariate analysis was performed, the small sample size was underpowered to show significant results, whereby models were limited

in both size and significance. Finally, other limitations also included missing data such as MRD status, comorbidities index for all patients and the use of TKIs as part of treatment course.

## CONCLUSION

AlloHCT has seen many advancements over the last decades allowing for significant improvements in acute leukemia patients outcome. The elderly population however has yet to take full advantage of these advancements, as treating physicians are sometimes reluctant to subject these patients to alloHCT due to their usual frailty, more aggressive disease with short life expectancy, and higher treatment-related mortality. We propose that alloHCT is feasible in this subgroup with over 50% 2-year OS in patients with favorable outcome predictive-factors such as achieving CR1, good functional status and donor CMV negativity. Interestingly, donor choice did not have a notable impact on outcome, albeit CMV positivity might confer worse survival, making any available donor a suitable candidate. These results can hopefully help guide decision-making regarding undergoing alloHCT in older patients pending prospective trials to confirm these findings. It is worth noting that non-chemotherapy-based novel immunotherapies such as BITE antibodies, inotuzumab, and CAR T-cells are potentially good alternatives to alloHCT when available and should also be considered in such patients.

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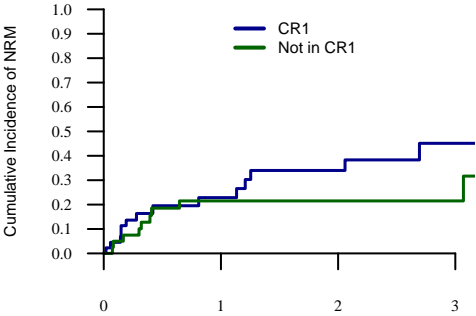
## AlloHCT in elderly ALL patients

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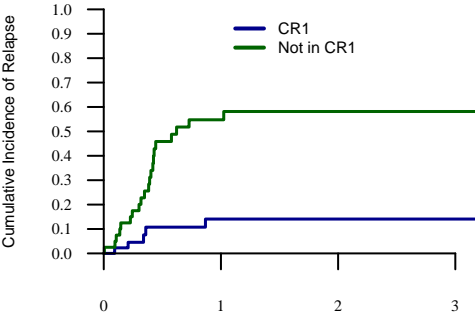
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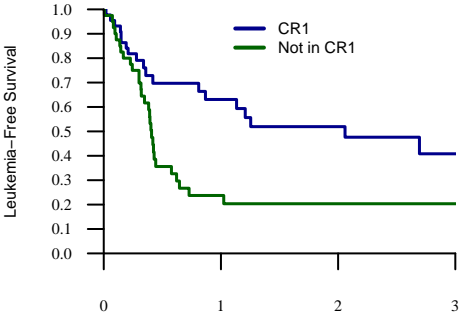
# NRM



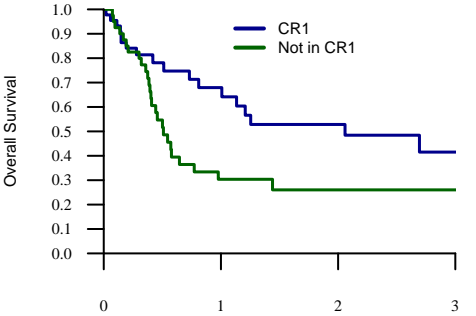
# RI



# LFS



# OS



n=84	
Patient Characteristics	N (%) / Median (Range) [IQR]
Age (years)	71.5 (70-83.8) [70.5-72.9]
Year of Transplant	2015 (2002-2019)
Follow-up (months)	23.2 [6.1-45.8]
Gender	
Male	48 (57.1%)
Female	36 (42.9%)
Diagnosis	
Ph- B-ALL	18 (21.4%)
Ph+ B-ALL	29 (34.5%)
Ph-unknown B-ALL	26 (31.0%)
T-ALL	11 (13.1%)
missing	13 (15.5%)
Status at transplant	
First CR	44 (52.4%)
CR2+	22 (26.2%)
Advanced	18 (21.4%)
Karnofsky score	
<90	32 (38.1%)
>=90	46 (54.8%)
missing	6 (7.1%)
HCT-CI	
HCT-CI = 0	31 (36.9%)
HCT-CI = 1 or 2	9 (10.7%)
HCT-CI >=3	14 (16.7%)
missing	30 (35.7%)
Patient CMV serology	
CMV-	27 (32.1%)
CMV+	57 (67.9%)

Table 1: Patient characteristics. Ph= Philadelphia; CR= Complete remission; HCT-CI= Hematopoietic Cell Transplantation-Comorbidity Index; CMV= Cytomegalovirus.

n=84	
Transplant Characteristics	N (%) / Median (Range) [IQR]
Diagnosis to transplant (months)	8.8 (2.1-101) [5.7-16.3]
Donor	
Matched sibling	19 (22.6%)
Unrelated	49 (58.3%)
Haploidentical	14 (16.7%)
Cord blood	2 (2.4%)
Source of stem cells	
Bone marrow	13 (15.5%)
Peripheral blood	69 (82.1%)
Cord blood	2 (2.4%)
Donor Gender	
Male	55 (65.5%)
Female	25 (29.8%)
missing	4 (4.8%)
Female to male	
No	69 (82.1%)
Yes	13 (15.5%)
missing	2 (2.4%)
Donor CMV serology	
CMV-	36 (42.9%)
CMV+	47 (56.0%)
missing	1 (1.1%)
In vivo T-Cell Depletion	
No	38 (45.2%)
Yes	46 (54.8%)
Conditioning	
MAC	19 (22.6%)
RIC	65 (77.4%)
MAC Chemo	3 (3.6%)
RIC Chemo	47 (55.9%)
MAC TBI	16 (19.0%)
RIC TBI	18 (21.5%)
Post-transplant cyclophosphamide	
No	67 (79.8%)
Yes	16 (19.0%)
missing	1 (1.2%)

**Table 2: Transplant characteristics.** CMV= Cytomegalovirus;  
MAC= Myeloablative conditioning; RIC= Reduced intensity

Cause of death	n=46 N (%)
Original disease	19 (41.3%)
Infection	12 (26.1%)
GVHD	4 (8.7%)
Interstitial pneumonitis	3 (6.5%)
Multi-organ failure	2 (4.3%)
Other transplant related	1 (2.2%)
Failure/Rejection	1 (2.2%)
Missing	4 (8.7%)

Table 3: Cause of death.

		2 year				
		Relapse	NRM	LFS	OS	GRFS
Whole population		36.6%[25.3-48]	28%[17.8-39.1]	35.4%[24-47]	38.6%[26.6-50.5]	23.1%[13.5-34.2]
Status at transplant	CR1	14.1%[4.9-27.9]	34%[18.2-50.5]	51.9%[33.6-67.5]	52.8%[33.9-68.6]	36%[19.7-52.7]
	CR2+	53.9%[27-74.7]	24.8%[8.4-45.6]	21.3%[6.1-42.7]	33.1%[13.8-54]	7.5%[0.6-27.5]
	Advanced	64.4%[34.9-83.2]	17.2%[3.8-38.7]	18.3%[4.6-39.4]	20.6%[5.2-43]	12.7%[2.2-33]
	P value	0.001	0.5	0.009	0.029	0.01
Diagnosis	Ph- B ALL	24.2%[6.7-47.6]	37.9%[14-61.9]	37.9%[14.9-61]	37.2%[14.4-60.4]	29.5%[8.7-54.3]
	Ph+ B ALL	30.7%[14.1-49]	27.8%[11.6-46.6]	41.6%[22.2-59.9]	41.9%[21.7-60.8]	25.6%[9.9-44.8]
	T ALL	68.8%[15.3-92.8]	0%	31.2%[4.6-64.3]	30.3%[4.4-63.3]	17.7%[1-52.2]
	P value	0.28	0.11	0.73	0.55	0.13
	All B ALL	28.9%[15.8-43.4]	32.9%[18.3-48.3]	38.2%[22.8-53.4]	37.5%[21.8-53.3]	24.5%[11.3-40.3]
Age at transplant	< Median	35.8%[20.2-51.7]	15%[5.9-28]	49.2%[31.9-64.3]	49.3%[31.5-64.8]	28.4%[13.8-45]
	> Median	37.7%[21.4-53.9]	40.4%[23.2-57]	22%[9.4-37.8]	27.8%[13.2-44.5]	18.4%[7.3-33.4]
	P value	0.8	0.06	0.2	0.3	0.92
Donor	Matched sibling	18.4%[3.9-41.3]	30.8%[7.5-58.7]	50.8%[21.1-74.4]	48.3%[19.5-72.3]	47.8%[20.2-71.2]
	Unrelated	38.7%[24.2-53]	29.2%[16.4-43.2]	32.1%[18.8-46.3]	36.2%[21.7-50.8]	15.5%[6.1-29]
	Haploidentical	55.9%[18.5-81.8]	11%[0.4-41.2]	33.1%[8.1-61.4]	40.2%[10.9-68.7]	21.4%[3.5-49.3]
	P value	0.21	0.64	0.42	0.52	0.08
Karnofsky	<90	24.2%[10.2-41.2]	44.3%[25.1-62]	31.5%[15.4-49.1]	34.4%[17.3-52.2]	19.3%[7.3-35.6]
	>=90	45.5%[29.4-60.3]	16.7%[7-30]	37.8%[22.7-52.7]	40.7%[24.7-56.2]	27.7%[14.7-42.4]
	P value	0.07	0.016	0.61	0.42	0.92
HCT-CI	0	29.8%[13.6-48]	28.6%[13-46.4]	41.6%[22.9-59.4]	44.3%[24.9-62.1]	24.6%[10.3-42.1]
	1 or 2	38.9%[6-72.9]	36.1%[1.1-79.6]	25%[1.4-63.9]	25%[1.4-63.9]	26.7%[1.5-65.9]
	>=3	42.7%[10.1-72.9]	22.9%[2.8-54.4]	34.4%[8.2-63.4]	29.6%[5.2-60.7]	21.4%[3.5-49.3]
	P value	0.64	0.68	0.87	0.88	0.86
Year of transplant	< Median	38.4%[20.5-56.1]	36.1%[18.2-54.3]	25.5%[11-42.9]	29.9%[13.8-47.8]	25.9%[11.4-43.2]
	> Median	36%[21.4-50.8]	22.7%[11.3-36.5]	41.3%[25.9-56.1]	44.6%[28.5-59.4]	20%[8.3-35.4]
	P value	0.47	0.55	0.12	0.3	0.7
Conditioning	MAC	37.4%[13.9-61.3]	15.8%[3.7-35.6]	46.8%[21.7-68.5]	44.2%[19.3-66.7]	43.7%[20.2-65.2]
	RIC	36%[23.4-48.8]	30.7%[18.8-43.5]	33.3%[20.9-46.1]	37.6%[24.2-51]	19.5%[9.9-31.5]
	P value	0.72	0.65	1	0.85	0.74
TBI	No	32.7%[18.9-47.2]	30.4%[17-44.9]	36.9%[22.3-51.6]	37.2%[22.2-52.1]	27.4%[15-41.2]
	Yes	43.7%[23.9-62]	24.4%[9.9-42.4]	31.9%[14.8-50.5]	41.5%[22-59.9]	14.7%[3.1-34.7]
	P value	0.41	0.88	0.52	0.87	0.47
Patient sex	Male	36.4%[20.9-52.1]	26.1%[13.6-40.4]	37.5%[22.1-53]	38%[22-53.9]	21.8%[9.5-37.2]
	Female	37.1%[20.6-53.6]	29.1%[14-46.2]	33.8%[17.8-50.6]	39.6%[21.9-56.8]	24.3%[10.9-40.6]
	P value	0.99	0.72	0.6	0.4	0.9
Donor sex	Male	30.1%[17.3-43.9]	29.3%[16.8-43.1]	40.6%[26-54.7]	44.3%[29.3-58.3]	29.8%[17-43.6]
	Female	46.1%[23.6-66.1]	24.1%[7.8-45.2]	29.8%[11.7-50.4]	28.6%[10.2-50.4]	9.5%[0.8-31.3]
	P value	0.2	0.45	0.63	0.57	0.37
Female to male transplant	No	33.8%[21.9-46.1]	28.7%[17.4-40.9]	37.6%[24.9-50.2]	42.3%[28.8-55.1]	26.1%[15.3-38.3]
	Yes	58.2%[17.7-84.5]	15.4%[2.2-40.1]	26.4%[4.6-56.1]	17.3%[1.1-50.2]	24.6%[4.8-52.4]
	P value	0.09	0.42	0.34	0.25	0.33
Patient CMV	CMV-	35.8%[13.3-59.2]	25.3%[7.6-48]	38.9%[15.9-61.7]	47.3%[20.9-69.9]	18.5%[3.6-42.4]
	CMV+	38.1%[24.8-51.2]	28.7%[17-41.6]	33.2%[20.7-46.2]	35.2%[22.2-48.5]	26.5%[15.2-39.2]
	P value	0.37	0.81	0.23	0.25	0.9
Donor CMV	CMV-	20.8%[8.1-37.5]	30.1%[14.3-47.7]	49%[29.5-66]	54.6%[33.8-71.3]	25.1%[9.8-43.9]
	CMV+	49.9%[33-64.7]	26.9%[14-41.6]	23.2%[11.1-37.9]	25.2%[12.5-40.2]	18.8%[8.2-32.6]
	P value	0.007	0.65	0.012	0.024	0.27
In vivo T-cell depletion	No	39.2%[21.2-56.9]	23.9%[9.9-41.2]	36.9%[19.2-54.7]	47.3%[27.2-65]	29%[13.7-46.3]
	Yes	34.4%[20-49.2]	31.6%[17.7-46.5]	34.1%[19.7-49]	32.8%[18.5-47.9]	19.8%[8.8-33.9]
	P value	0.54	0.92	0.75	0.65	0.92

Table 4 : Univariate analysis. CR= Complete remission; Ph= Philadelphia; MAC= Myeloablative conditioning; RIC= Reduced intensity conditioning; CMV= Cytomegalovirus; TBI=Total Body Irradiation.

		180 days		2 year	
		Acute GVHD II-IV	Acute GVHD III-IV	chronic GVHD	ext. chronic GVHD
Whole population		29.6%[20.1-39.8]	9.9%[4.6-17.6]	33.6%[21.7-46]	23.3%[12.9-35.4]
Status at transplant	CR1	29.2%[16.1-43.6]	4.8%[0.8-14.3]	33.3%[16-51.7]	29.3%[13.2-47.4]
	CR2+	36.4%[16.9-56.3]	18.2%[5.5-36.8]	55.6%[27.4-76.7]	34.1%[10.3-60.2]
	Advanced	29.4%[10.1-52]	11.8%[1.8-32]	7%[0.3-28.8]	0%
	P value	0.9	0.24	0.013	0.08
Diagnosis	Ph- B ALL	27.8%[9.6-49.7]	5.6%[0.3-23.1]	13.9%[1.8-37.9]	9.5%[0.3-37.7]
	Ph+ B ALL	29.6%[13.8-47.4]	11.1%[2.7-26.2]	41.7%[19.5-62.7]	27.8%[10.5-48.5]
	T ALL	45.5%[14.9-72.2]	18.2%[2.4-45.7]	44.3%[4-81.3]	44.3%[4-81.3]
	P value	0.53	0.55	0.18	0.09
	All B ALL	28.9%[16.4-42.6]	8.9%[2.8-19.5]	30.9%[16-47.1]	20.8%[8.7-36.5]
Age at transplant	< Median	33.2%[18.8-48.2]	12.5%[4.5-24.8]	34.4%[17.6-51.8]	27.5%[12.6-44.8]
	> Median	29.3%[16.2-43.6]	7.3%[1.9-18]	32.6%[16.1-50.2]	18.3%[6.2-35.5]
	P value	0.69	0.42	0.76	0.54
Donor	Matched sibling	22.2%[6.5-43.6]	5.6%[0.3-23.2]	16.3%[2.1-42.6]	10.2%[0.4-38.5]
	Unrelated	29.6%[17.2-43.1]	6.2%[1.6-15.6]	41.9%[25.2-57.7]	31.7%[17.1-47.4]
	Haploidentical	42.9%[16.6-67.1]	28.6%[8.2-53.3]	21.8%[1.8-56]	0%
	P value	0.45	0.04	0.28	0.11
Karnofsky	<90	29%[14.2-45.6]	6.5%[1.1-18.9]	44.8%[24.9-62.8]	31.5%[14.4-50.2]
	>=90	32.4%[19.7-45.7]	12%[4.8-22.7]	21.6%[9.8-36.3]	14%[4.9-27.7]
	P value	0.84	0.41	0.18	0.26
HCT-CI	0	33.8%[17.3-51.2]	6.7%[1.1-19.5]	49.6%[28-67.9]	33.8%[15.6-53.2]
	1 or 2	22.2%[2.8-53]	0%	19%[0.3-62.4]	19%[0.3-62.4]
	>=3	50%[21.5-73.2]	35.7%[12.2-60.4]	14.9%[2.2-38.9]	0%[NaN-NaN]
	P value	0.35	0.015	0.32	0.13
Year at transplant	< Median	13.8%[4.2-28.9]	3.4%[0.2-15.3]	13%[3-30.7]	8.7%[1.3-25.1]
	> Median	40.9%[27.2-54]	13.5%[5.9-24.3]	46%[27.8-62.5]	32.7%[16.6-50]
	P value	0.016	0.15	0.018	0.054
Conditioning	MAC	38.9%[16.8-60.7]	16.7%[3.9-37.2]	26.5%[5-55.4]	7.4%[0.4-29.8]
	RIC	28.9%[18.2-40.6]	7.9%[2.9-16.3]	35.5%[21.9-49.3]	27.2%[14.8-41.2]
	P value	0.31	0.25	0.62	0.24
Patient sex	Male	37%[23.1-50.8]	8.7%[2.7-19.1]	33.5%[17.6-50.2]	20.9%[8-37.9]
	Female	23.2%[10.7-38.4]	11.4%[3.5-24.5]	33.3%[16.1-51.7]	26.2%[11.1-44.3]
	P value	0.19	0.66	0.76	0.4
TBI	No	25%[13.8-38]	8.3%[2.6-18.3]	36.6%[21.3-52]	24.7%[11.9-39.8]
	Yes	39.8%[22.9-56.3]	12.1%[3.7-25.8]	30.8%[10.6-54]	21.2%[5.3-43.9]
	P value	0.14	0.55	0.32	0.64
Donor sex	Male	31.5%[19.6-44.1]	7.4%[2.3-16.4]	37.3%[22.3-52.3]	22.8%[10.9-37.2]
	Female	33.7%[15.6-52.9]	16.7%[5-34.1]	30.7%[9-56]	27.8%[6.7-54.5]
	P value	0.78	0.21	0.38	0.93
Female to male transplant	No	30%[19.5-41.3]	7.5%[2.7-15.4]	35.6%[22.4-48.9]	24.5%[13.3-37.4]
	Yes	41.7%[13.9-67.8]	25%[5.4-51.7]	10%[0.4-38.2]	0%
	P value	0.34	0.07	0.49	0.48
Patient CMV	CMV-	41.7%[22.4-60]	11.1%[2.7-26.2]	55.4%[24.3-78.2]	56.7%[16.2-83.7]
	CMV+	25.9%[15.1-38.2]	9.3%[3.4-18.8]	22.6%[11.5-36]	11.1%[4-22.4]
	P value	0.18	0.82	0.007	0.001
Donor CMV	CMV-	37.7%[21.6-53.8]	11.4%[3.5-24.5]	43.4%[21.6-63.5]	36.9%[16.3-57.7]
	CMV+	24.4%[13-37.8]	8.9%[2.8-19.5]	25.2%[12.2-40.5]	14.4%[5-28.6]
	P value	0.27	0.73	0.29	0.1
In vivo T-cell depletion	No	41.1%[24.8-56.7]	13.5%[4.8-26.6]	38.3%[18.1-58.4]	17.8%[5.1-36.9]
	Yes	22.7%[11.6-36.1]	6.8%[1.7-16.9]	30.4%[16-46.2]	25.2%[12.1-40.5]
	P value	0.11	0.33	0.33	0.82

Table 5 : Univariate analysis. CR= Complete remission; Ph= Philadelphia; MAC= Myeloablative conditioning; RIC= Reduced intensity conditioning; CMV= Cytomegalovirus; TBI=Total Body Irradiation.

Outcome	Variables	HR (95% CI)	p value
Relapse	CR1 vs other	0.23 (0.08-0.67)	<b>0.007</b>
	MSD vs other	0.48 (0.13-1.77)	0.27
	Donor CMV positivity	2.87 (1.06-7.77)	<b>0.039</b>
	Year of HSCT	0.96 (0.84-1.10)	0.55
NRM	CR1 vs other	1.05 (0.43-2.58)	0.91
	MSD vs other	0.60 (0.20-1.85)	0.38
	KPS≥90	0.37 (0.15-0.88)	<b>0.025</b>
	Year of HSCT	0.91 (0.79-1.05)	0.18
LFS	CR1 vs other	0.49 (0.26-0.95)	<b>0.034</b>
	MSD vs other	0.54 (0.23-1.26)	0.16
	Donor CMV positivity	1.86 (0.97-3.58)	0.062
	Year of HSCT	0.95 (0.87-1.05)	0.3
OS	CR1 vs other	0.61 (0.32-1.20)	0.15
	MSD vs other	0.61 (0.26-1.41)	0.25
	Donor CMV positivity	1.96 (0.98-3.91)	0.057
	Year of HSCT	1.0 (0.91-1.11)	0.95
GRFS	CR1 vs other	0.54 (0.31-0.93)	<b>0.027</b>
	MSD vs other	0.54 (0.25-1.14)	0.1
	Year of HSCT	0.99 (0.91-1.08)	0.77
Acute GVHD II-IV	CR1 vs other	0.85 (0.39-1.86)	0.67
	MSD vs other	0.70 (0.24-2.06)	0.52
	Year of HSCT	1.10 (0.95-1.27)	0.22
Chronic GVHD	CR1 vs other	0.81 (0.32-2.04)	0.65
	MSD vs other	0.50 (0.11-2.21)	0.36
	Patient CMV positivity	0.44 (0.17-1.11)	0.08
	Year of HSCT	1.01 (0.82-1.23)	0.96

**Table 6: Multivariate Analysis.** HR: Hazard ratio. CI: Confidence interval. CR1: First complete remission. MSD: Matched sibling donor. HSCT: Hematopoietic stem-cell transplantation. NRM: Non-relapse mortality. KPS: Karnofsky score. LFS: Leukemia-free survival. OS: Overall survival. GRFS: GRFS and relapse free survival. GVHD: Graft-vs-host disease.