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OPTIMAL THRESHOLD AND TIME OF ABSOLUTE LYMPHOCYTE COUNT ASSESSMENT FOR OUTCOME PREDICTION AFTER BONE MARROW TRANSPLANTATION

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Abstract

PURPOSE: The recovery pace of absolute lymphocyte count (ALC) is prognostic after hematopoietic stem cell transplantation (SCT). Previous studies have evaluated a wide range of ALC cutoffs and time points to predict outcomes. We aimed to determine the optimal ALC measure for outcome prediction after SCT from bone marrow grafts (BMT).

METHODS: 518 patients who underwent BMT for acute leukemia or myelodysplastic syndrome between 1999 and 2010 were divided into training and test sets to assess the prognostic values of ALC on days 30, 60, 90, 120, 180, as well as, the first post-transplant day on which a patient achieved ALC of 100, 200, 300, 400, 500, and 1000/μL.

RESULTS: In the training set, the best predictor of overall survival (OS), relapse-free survival (RFS), and non-relapse mortality (NRM) was ALC on day 60. In the whole patient cohort, multivariable analyses demonstrated significantly better OS, RFS, NRM, and lower incidence of graft-versus-host disease among patients with ALC >300/μL on day 60, both including and excluding patients who had developed graft-versus-host disease prior to day 60. Among the patient-, disease-, and transplant-related factors assessed, only busulfan-based conditioning was significantly associated with higher ALC counts on day 60 in both cohorts.

CONCLUSION: The optimal ALC cutoff to predict outcomes after BMT is ALC of 300/μL on day 60 post-transplant.

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Keywords

Bone marrow transplantation; lymphocyte count; immune reconstitution

INTRODUCTION

Relapse, infectious complications, and graft-versus-host-disease (GVHD) are the major reasons for treatment failure after allogeneic hematopoietic stem cell transplantation (SCT). In the last decade, numerous attempts to reduce relapse incidence[1] and treatment-related morbidity/mortality associated with transplantation have been made[2, 3]. However, such interventions are costly and have side effects; therefore, they may be better suited for patients at high risk for treatment failure. One way high risk patients could be identified is by evaluating patients for a delay in immune reconstitution post-transplant, as it is an important cause of morbidity and mortality. Yet, most methods to assess immune recovery are complex, require special knowledge and are not part of clinical practice. Consequently, there is considerable need for a simple and reliable prognostic marker which will evaluate the recovery of immune function as a whole and can be widely used to identify the patients at high risk for treatment failure.

Immune reconstitution after SCT is a stepwise process where the innate immune system starts to recover before the adaptive system[4]. NK cells recover during the first weeks of transplant constituting the major part of the lymphocyte count early after transplant[5]. While thymus-independent donor memory T cells start expanding immediately after SCT, thymus-dependent development of new T cells from progenitors may take 1–2 years[6]. In addition, B cells are low in number at least during the first 2 months post-transplant[7] and reconstitution of the B compartment may take up to 2 years[8].

Patient age, in vivo or ex vivo T cell depletion, and donor type may affect immune reconstitution early after SCT[9, 10]. However, the most important factor affecting reconstitution is thought to be the type of the graft source[11]. Peripheral blood (PB) grafts contain approximately one log more lymphocytes compared to bone marrow (BM) grafts[12]. Consequently, absolute lymphocyte counts (ALC) after SCT are higher with PB compared to BM grafts[13, 14] and various T cell subsets, i.e. CD45RA+ naïve, reconstitute faster after SCT from PB grafts[11].

The lymphocytes reconstituting the recipient's immune system are crucial in preventing infectious complications and disease relapse, latter through graft-versus-tumor effect. ALC after SCT may be a surrogate marker for immune reconstitution and a predictor of these complications. Various studies have shown that a delayed recovery of lymphocytes after SCT increased non-relapse mortality (NRM) and relapse incidence (RI), shortening survival[13–27]. However, most of these studies included cohorts with few patients, proposed a wide range of arbitrary time points and thresholds with conflicting findings on relapse and survival, and incorporated SCTs from different graft sources (Table 1).

Here, we aimed to identify the optimal post-transplant ALC time point/cutoff that would best predict clinical outcomes in the early post-SCT period. This could be used to globally

assess the recovery of immune function and to possibly identify the high-risk patients for intervention.

PATIENTS and METHODS

Patients

Included in this study were all patients older than 18 years with acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), and myelodysplastic syndrome (MDS) who underwent a SCT with a BM graft (BMT) between 1999 and 2010 identified through the departmental registry. Demographics, disease characteristics, treatment, GVHD, cytomegalovirus (CMV), and survival data were retrieved from the departmental database and patient charts. ALC on days 30, 60, 90, 120, 180, as well as the first post-transplant day on which a patient achieved ALC of 100, 200, 300, 400, 500, and 1000/μL were collected from the institutional laboratory information system through a computer algorithm developed specifically for this study to minimize human error.

Patients were managed clinically according to institutional guidelines including infection prophylaxis for Pneumocystis carinii, herpes viruses, and fungus. CMV reactivation was monitored by CMV pp65 antigenemia assay or CMV PCR from peripheral blood. Preemptive therapy was instituted in patients with documented CMV viremia. Patients received G-CSF beginning at day +7 after transplantation. GVHD was diagnosed clinically, confirmed pathologically whenever possible, and classified according to standard criteria[28]. GVHD diagnosed after day 100 post-transplant was classified as chronic GVHD. Only patients who engrafted were evaluable for GVHD assessment. Donor-recipient human leukocyte antigen (HLA) matching was established by DNA sequence-specific oligonucleotide typing for HLA-A, -B, -Cw, -DQB1, and - DRB1 loci. Donors were HLA matched related, unrelated or haploidentical.

Definitions

A haploidentical donor was defined as a related donor with ≥2 HLA allele mismatches in the same haplotype. Complete remission was defined as ≤5% blasts in bone marrow, absence of blasts in peripheral blood, platelet count ≥100K/L, and absolute neutrophil count ≥1000/L. Overall survival (OS) and relapse-free survival (RFS) were defined as the time from BMT until death from any cause, and disease relapse or death, respectively. NRM was defined as death in a patient without leukemia relapse. Other time-to-event measures (relapse, CMV reactivation, acute and chronic GVHD) were computed from date of BMT to date of event.

Statistical Methods

To determine the optimal ALC threshold, the dataset was first divided into a training set (70% of the data) and test set (remaining 30%) by random assignment. The application Cutoff Finder[29] was used to find the optimal cutoff point of each ALC measure for OS, RFS, NRM, and relapse on the training set (based on a univariate Cox proportional hazards regression model). The determined cutoff value was then used to dichotomize patients in the test set and a univariate Cox proportional hazards regression model was used to determine the association between the outcome measure and the dichotomized group. To determine the

robustness of the estimates, 1,000 bootstrap samples from the test set were created. A Cox proportional hazards regression model was performed on each bootstrapped sample and the mean and 95% confidence interval of the distribution of hazard ratios were computed. Lastly, the percentage of the bootstrapped samples with p-values less than 0.05 (from the Cox model) was computed (power).

To assess the factors affecting ALC, the whole cohort was grouped by the determined optimal ALC cutoff value and assessed using Pearson's chi-square test (categorical measures) and Wilcoxon rank sum test (age at SCT). OS estimates were determined using the Kaplan-Meier method and difference between ALC groups was assessed using the log-rank test. Associations between measures of interest and OS/RFS were assessed in the whole patient cohort using Cox proportional hazards regression models. The cumulative incidence of relapse (RI), NRM, GVHD, and CMV was determined using the competing risks method. The competing risk included for relapse was death before progression and the competing risk included for NRM was relapse. For GVHD and CMV, the competing risks included were relapse and death. For all outcomes, patients who experienced the event before the determined ALC cutoff day were excluded from that outcome analyses and patients who did not experience the event were censored.

All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC). All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

RESULTS

Among 518 patients included in the study, median ALC on days 30, 60, 90, 120, and 180 were 375/μL, 540/μL, 610/μL, 685/μL, and 835/μL, respectively. The optimal ALC cutoff values with the highest power for OS, RFS, relapse, and NRM prediction are presented in Table 2 (the measures that were not found to be significantly associated with outcomes are not shown). The distribution of hazard ratios for OS according to different cutoff levels of ALC on day 60 is demonstrated in Figure 1. Of those, the measures with the best prediction of OS and RFS were days 60, 120, and 180. Only ALC measures at days 30 and 180 were associated with time-to-relapse in the training set. However, neither was found to be significant in the test set. Consistent with OS and RFS, the ALC on day 60 produced the best results for NRM with a power > 99% albeit at a different ALC cutoff. The time to achieve an ALC of 100, 200, 300, 400, 500 or 1000/μL were not found to significantly affect clinical outcomes. ALC on day 60 was chosen as the optimal threshold over days 30, 120, and 180 because: 1) Day 60 measure had the highest power to detect NRM; 2) Day 30 had lower power to predict OS and its association with relapse was not confirmed in the test set; 3) Compared to days 120 and 180, i) the hazard ratios from the training and test sets as well as the bootstrapped samples were more consistent at day 60 and ii) earlier prediction could be clinically more useful.

In the whole patient cohort, 102 of 134 (76%) patients with ALC ≤ 300/μL and 173 of 353 (49%) patients with ALC >300/μL on day 60 died. The identified primary causes of death are presented in Table 3. While 14% and 17% of patients with ALC ≤ 300/μL on day 60 died

from acute and chronic GVHD, 1% and 5% of patients with ALC >300/μL died from the same causes. A significantly increased risk in OS and RFS in addition to increased NRM and decreased RI was seen in the univariate analyses in patients with ALC ≤ 300/μL compared to those with >300/μL on day 60 (Figure 2). These results were maintained after controlling for clinical factors in multivariable analyses (Table 4). Patients with ALC >300/μL experienced significantly less acute GVHD (aGVHD). In addition, there was a significant association between ALC group and aGVHD grade II-IV (HR [95% CI]:0.30 [0.14 – 0.68]; p=0.004) but not with aGVHD grade III-IV. There was no significant association between ALC and chronic GVHD (cGVHD) and CMV incidence in univariate or multivariable analyses. While the remission status at the time of BMT and busulfan-based conditioning regimen were the only other significant measures associated with OS and RFS; age, donor HLA-match, and use of anti-thymocyte globulin (ATG) or alemtuzumab were other factors affecting NRM. To assess the potential confounding effect of corticosteroid treatment for aGVHD, we repeated the multivariable outcome analysis after excluding patients who had developed aGVHD prior to day 60. These verified the significant improvement of OS, RFS, and NRM with higher ALC, while RI was no longer associated with ALC.

Patient age, diagnosis, donor type, remission status at the time of BMT, ATG/alemtuzumab use, post-BMT cyclophosphamide use, graft total nucleated, CD34+, and CD3+ cell counts were not associated with whether a patient had ALC above or below 300/μL on day 60 (Table 5). In a separate analysis, ATG/alemtuzumab was not found to be associated with ALC recovery on day 30, either. TBI-based conditioning was significantly associated with lower ALC on day 60, however, this did not remain significant when patients who developed aGVHD before day 60 were excluded from analysis (p=0.138). Busulfan based conditioning was significantly associated with higher ALC counts on day 60 both including and excluding patients developing aGVHD prior to day 60.

DISCUSSION

The advent of post-SCT early interventions tackling relapse and NRM before they occur necessitates a practical and reliable prognostic marker to select high-risk patients for these costly procedures. ALC recovery pace may be such a marker as it has been shown to be associated with improved clinical outcomes. However, studies to date could not determine the optimal ALC threshold because of 1) small cohort size, 2) heterogeneity of the graft sources and the diseases in their cohorts, and 3) lack of a robust statistical methodology. In this study, we confirmed the positive impact of early lymphocyte recovery on survival and NRM after BMT, and determined the optimal ALC threshold for outcome prediction to be 300/μL on post-BMT day 60.

To our knowledge, among the studies assessing post-SCT ALC recovery, ours has the largest cohort that includes SCTs solely from a single graft source. We believe it was essential to include only one graft source because optimal prognostic ALC thresholds could vary between different graft types. The lymphocyte repopulation kinetics is significantly different between the PB and BM grafts[11] likely due to the one log difference in their lymphocyte contents[12]. Accordingly, while Michelis et al. found that 58% of patients who underwent

SCT from PB grafts achieved ALC of 500/μL by day 30, in our study median ALC on day 30 was only 375/μL. We chose to study SCTs from BM grafts which have a slower lymphocyte recovery pace while a follow-up study using PB grafts is planned.

Our study is also the first to methodologically analyze broad ALC measures to determine the most prognostic measure. After finding the optimum cutoff ALC level for each post-SCT day and verifying their prognostic significance in a separate test set, we also analyzed the time to achieve specific ALC levels but these were not found to be prognostic. While we studied ALC on various days from 30 to 180, most of the previous studies had used ALC on days 21–3014, 15, 17, 18, 20–22, 24–26 indirectly assessing NK cell recovery as NK cells are the dominant lymphocyte subset 3–4 weeks after SCT[30, 31]. Among the few studies assessing the impact of ALC after day 30[13, 16, 19], only Kim et al. used a methodology - restricted cubic spline smoothing method- to assess different ALC cutoff levels[13]. However, instead of individually calculating HRs for each different ALC cutoff level, Kim et al. performed one analysis in which ALCs on day 30 were stratified into five comparison (0–200, 200–300, 300–400, 400–500, >2600) and one reference arm (500–2600). ALC of 200 was chosen to assess outcomes since it was significantly higher than the reference group. This cutoff level was also used for days 60 and 90. Given that potential cutoff levels for days 60 and 90 were not assessed, the optimal ALC cutoff level with the highest power for prognostication may not have been identified in that study.

We found the optimal time point to assess ALC to be day 60. The power to predict OS, RFS, and NRM was significantly higher for day 60 than for day 30 which most of previous studies used as the time point to assess ALC recovery. However, our study cohort comprised SCTs solely from BM grafts whereas others included both PB and BM sources (Table 1). It is possible that the optimal time point for PB grafts would be earlier than day 60 due to faster recovery of lymphocytes after SCT with PB grafts. Similar to our study, the few studies assessing extended days found higher ALC on days 60, 90 and 100 were also associated with improved survival and NRM[13, 16, 19].

While further studies are needed, the improved survival and NRM with faster ALC recovery is likely related to a lower incidence of GVHD and infectious complications, as previously observed by us[32]. However, we did not detect any significant difference in CMV reactivation incidence between the low and high ALC groups although previous studies had shown an inverse relationship between lymphocyte recovery pace and infection rates[14, 33]. Moreover, in the present study we had ruled out the confounding effect of corticosteroids used in the treatment of aGVHD by demonstrating the same outcome results after excluding the patients who had developed aGVHD prior to ALC measurement time point of day 60. Another explanation could be a lower incidence of GVHD with faster ALC recovery. Similar to Rigoni et al.'s report of a significantly lower aGVHD incidence in patients with ALC >300 on day 30[15], we also observed a lower incidence of aGVHD in patients with ALC > 300 on day 60. Moreover, higher ALC at the time of aGVHD diagnosis was previously shown to be associated with better prognosis[34] and may have played a partial role in improved survival and NRM in our study.

Various patient/donor, disease, graft, and transplant characteristics were reported to be associated with immune recovery pace after SCT. Klyuchnikov et al. summarized these findings in their paper[35]. In our cohort, busulfan- and TBI-based conditioning were the only two clinical characteristics associated with ALC recovery, although TBI-based conditioning was not significantly associated with ALC recovery when patients who experienced aGVHD prior to day 60 were excluded from the analysis. Previous studies had suggested that the graft source was the most important factor affecting ALC recovery – faster after SCTs from PB compared to those from BM and umbilical cord blood[11, 36, 37] Hence, we opted to include SCTs from a single graft source in our cohort. ATG was previously reported to slow CD4+ T cell recovery but improve B cell and NK cell recovery[38]. We did not observe slow ALC recovery in patients treated with ATG or alemtuzumab. While there are conflicting reports on the impact of patient age and donor type on the recovery of ALC and certain lymphocyte subsets[9–11, 35, 39], we did not observe such impact on ALC recovery.

Our study is limited by its retrospective nature. We attempted to limit human error in data collection by retrieving ALC electronically from the laboratory information system with the help of a computer algorithm. Second, this is a single center study and results may not apply to other centers with different standards, algorithms, and patient population. Eighty percent of the SCTs in our cohort were from unrelated donors, and 53% of the remaining SCTs were from haploidentical donors. The ideal ALC cutoff may differ in centers primarily using bone marrow grafts for related donors. Third, although we chose to assess ALC as a prognostic marker to identify high-risk patient groups, there may be more powerful assays such as certain lymphocyte subset counts. For instance, NK cell count may correlate more with RI and CD4+ T cell count may be a better predictor for infectious complications. Fourth, while ours and several other studies demonstrated association between ALC recovery and NRM, this does not prove causality. The studies to date show prognostic value of ALC but this may not confer to a predictive value for an early prevention method. Finally, our results are limited to BMTs and should not be employed for SCT from PB grafts as the optimal cutoff is very likely to be on an earlier timepoint than day 60. A separate study is needed for those patients.

In conclusion, we determined the optimal ALC cutoff to predict outcomes after BMT to be ALC of 300/μL on post-transplant day 60. This was significantly associated with survival and NRM. We believe patients with ALC lower than 300 on day 60 should be targeted for morbidity prevention. Further studies are needed to determine a cutoff for SCT from PB grafts and to verify our findings in multi-center cohorts.

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Highlights

- Day 60 absolute lymphocyte count (ALC) of 300/μL is the optimum prognostic threshold
- Patients with ALC >300 on day 60 have better OS, RFS, NRM, and less GVHD
- Conditioning regimen may influence lymphocyte recovery after marrow transplantation

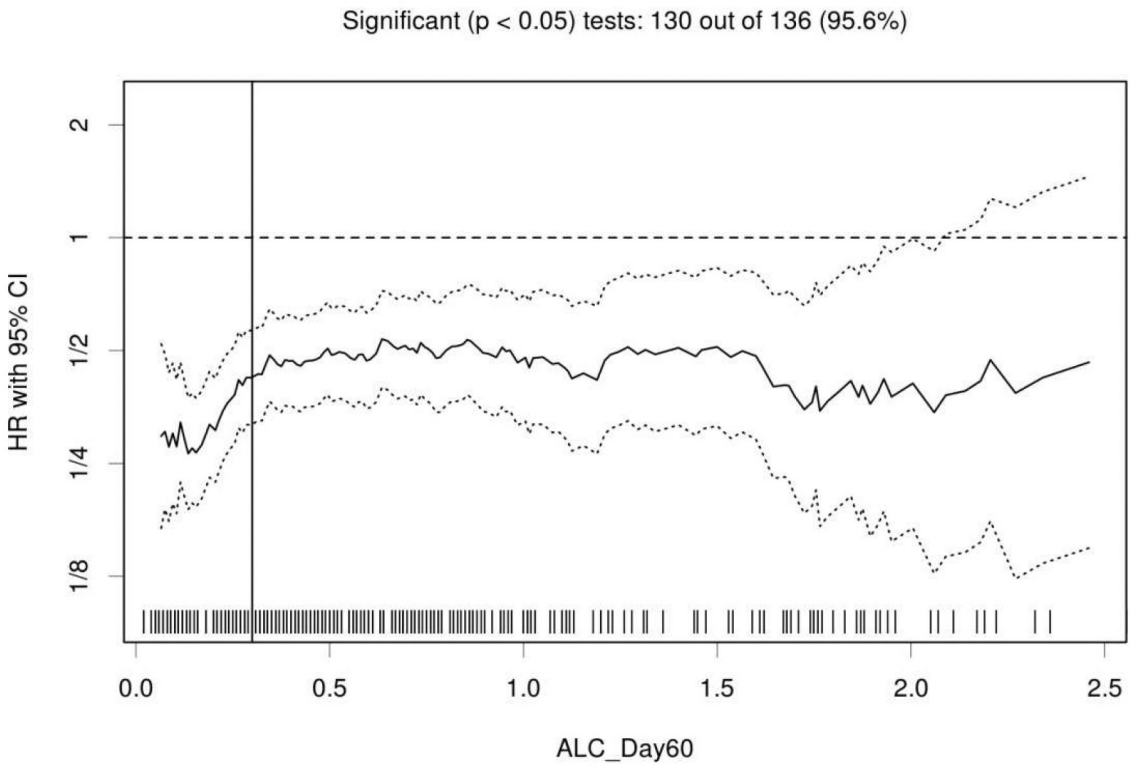

Figure 1 -

Distribution of Hazard ratios for overall survival according to different cutoff levels of absolute lymphocyte count on post-transplantation day 60

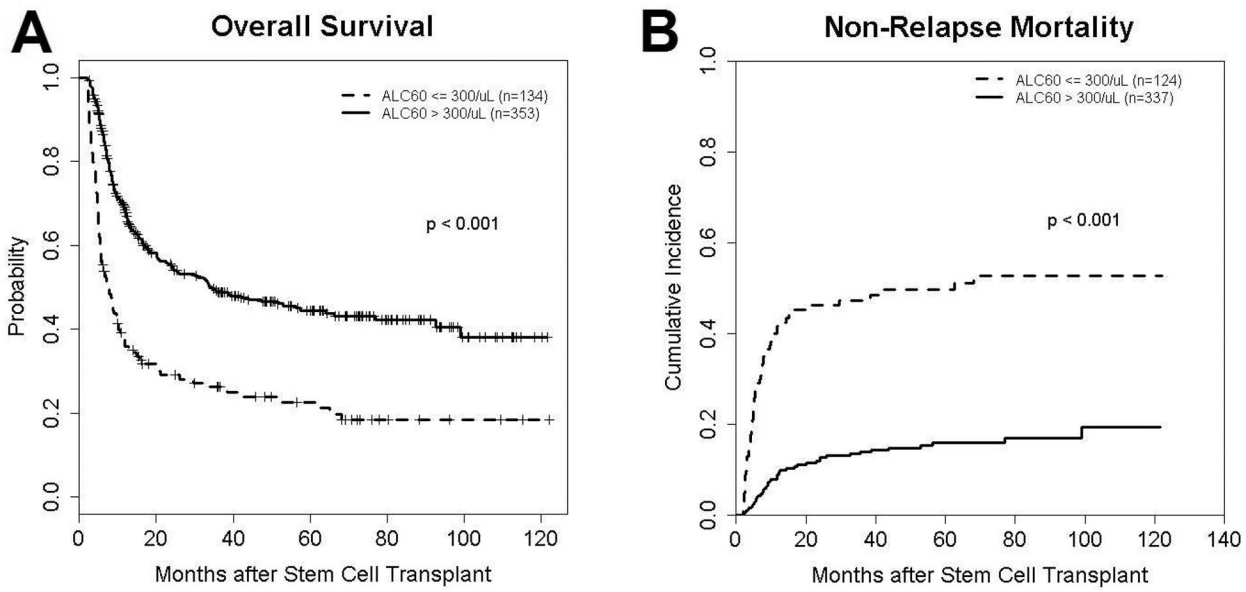

Figure 2 -

Kaplan-Meier curve of overall survival (A) and cumulative incidence curve of non-relapse mortality (B) in high (>300/μL on day 60) and low ALC (≤300/μL) groups in the whole patient set

Table 1 -

Studies published to date assessing the association of post-transplantation absolute lymphocyte counts (ALC) with clinical outcomes

Study (year)	Patient characteristics	ALC timepoint and cutoffs assessed and rationale for their selection	OS	RFS	NRM	RI	aGVHD	cGVHD
Rigoni L, 2015[15]	100 chemo-responsive AML/ALL/MDS pts. All sources and donors. 78% MA, 22% RIC	Timepoints and cutoff arbitrarily chosen	OS longer in high ALC group. HR:		HR:			
		300@d21 (30%)	1.3 (0.7–2.6)		1.2(0.6–2.6)	25% vs. 26% (NS)	76% vs. 52% (NS)	33% vs. 36% (NS)
		300@d30 (18%)	2.2 (1.0–4.7)		2.0 (0.9–4.4)	12% vs. 29% (NS)	94% vs. 50% (0.003)	46% vs. 34% (NS)
Kim HT, 2015[13]	1109 pts. All diseases. UCB and haplo excluded. 48% MA, 52% RIC	Timepoints arbitrarily, cutoff b/o RFS curves	At 5 yr:	At 5 yr:	At 5 yr:	pts with <200 at any time point (14% of all pts) vs. >200 at m1, m2 and m3: 40% vs. 43% (NS)		
		200@m1 (8%)	30% vs. 45% (<0.001)	19% vs. 38% (<0.001)	33% vs. 20% (0.002)			
		200@m2 (6%)	28% vs. 49% (<0.001)	25% vs. 41% (<0.001)	44% vs. 19% (<0.001)			
		200@m3 (6%)	27% vs. 53% (<0.001)	22% vs. 45% (<0.001)	41% vs. 18% (<0.001)			
Yamamo to, 2014[16]	206 AML/ALL/MDS pts. MA and RIC. All sources and donors	Timepoint d100 selected to exclude aGVHD effect. Cutoff b/o OS curves	OS longer in high ALC group. HR:		NRM lower in high ALC group. HR:			
		500@d100 (18%)	2.4 (1.3–4.5)		2.8 (1.1–6.8)	1.4 (0.7–3.0)		
Michelis FV, 2014[17]	191 AML pts in CR. MRD or MUD. PB only. MA and RIC	Cutoff arbitrarily chosen. Timepoint b/o the median # of days to achieve ALC500				RI lower in high ALC group		
		500@d28 (42%)	NS in MVA		NS in MVA	0.49 (0.26–0.92)		
Han DK, 2013[18]	69 children with heme malignancies. 64 MA, 5 RIC. All sources and donors	Cutoff b/o prelim analyses between ALC200, 300, 400, 500	At 5 yr:		At 5 yr	At 5 yr:	GII-IV incidence:	Extensive
		500@d21 (41%)	62% vs. 67% (NS)		19% vs. 16% (NS)	20% vs. 22% (NS)		14% vs. 15% (NS)

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2020 March 31.

Study (year)	Patient characteristics	ALC timepoint and cutoffs assessed and rationale for their selection	OS	RFS	NRM	RI	aGVHD	cGVHD
		500@d30 (28%)	53% vs. 71% (0.043) (NS on MVA)		34% vs. 11% (0.019	20% vs. 22% (NS)	29% vs. 17% (NS)	11% vs. 16% (NS)
DeCook LJ, 2012[19]	118 pts with heme malignancies. RIC with Flu/Mel. PB and BM. All donors	Rationale not provided	UVar OS analyses: On MVar only d100 was sig (0.049)					
		300@d15 (57%)	0.25					
		300@d30 (6%)	<0.001					
		300@d60 (11%)	<0.001					
		300@d100 (18%)	<0.001					
Le Blanc K, 2009[20]	102 pts AML-CML-MDS only, MA only, MUD only, PB and BM	MVarA performed with ALC on day 30 as a continuous variable. d30 chosen b/o previous studies	NS on MVarA	sig increases with ALC (0.04)	sig decreases with ALC (<0.05)			
Afzal S, 2009[21]	71 children with AML in CR. All sources.	Rationale not provided			At 3 yr:	At 3 yr:	G III-IV:	Extensive:
		300@d21			14% vs. 27% (NS)	25% vs. 20% (NS)	16% vs. 12% (NS)	18% vs. 13% (NS)
		300@d30			21% vs. 13% (NS)	21% vs. 26% (NS)	18% vs. 16% (NS)	21% vs. 11% (NS)
Ishaqi MK, 2008[22]	132 children with ALL in CR. All sources. MA only	Rationale not provided		At 3 yr:	At 3 yr:	At 3 yr:	G III-IV:	Extensive:
		300@d21		42% vs. 66% (0.02)	17% vs. 19% (NS)	40% vs. 10% (0.002)	32%−24% (NS)	13% vs. 12% (NS)
		300@d30		30% vs. 57% (<0.001)	25% vs. 14% (NS)	46% vs. 26% (0.01)	31% vs. 29%	19% vs. 9% (NS)
Savani BN, 2007[23]	160 pts with leukemia after TCD from MRD with MA. BM and PB grafts	d30 chosen as a marker for NK cells.Cutoff b/o median ALC on d30	OS longer in high ALC group		NRM lower in high ALC group	Worsening effect of low ALC seen only in AML/MDS but not in ALL pts	Low ALC a/w more aGVHD.G II-IV:	High ALC a/w more cGVHD
		450@d30	2.7 (1.03–5.1)		3.6 (1.2–10.6)	3(1.5–6)	1.8 (1.1–2.9)	0.55 (0.34–0.87)
Kim DH, 2004[14]	82 pts with heme malignancies. MA and RIC. BM and PB grafts. All donors	d21 chosen because it was an early timemark. Rationale for ALC cutoff not provided	OS longer in high ALC group	RFS longer in high ALC group	At 1 yr:	RI lower in high ALC group		

Study (year)	Patient characteristics	ALC timepoint and cutoffs assessed and rationale for their selection	OS	RFS	NRM	RI	aGVHD	cGVHD
		350@d21	2.7 (1.2–6.0)	2.8 (1.4–5.8)	52% vs. 31% (NS)	2.5 (1.1–6.2)		
Kumar S, 2003[24]	43 pts with ALL; MA only; BM only	Assessed measures: ALC@d21 => 150, 175, 200, 225 ALC@d30 => 150, 175, 200, 225		RFS longer in high ALC group		RI lower in high ALC group		
		175@d21		p = 0.0028		4.5 (1.2–16.6)	NS	NS
Chakrabarti S, 2003[25]	29 pts with heme malignancies. TCD BM or PB followed by TCAB. UCB and haplo excluded	Timepoint chosen arbitrarily. Cutoff b/o median ALC on d30	OS longer in high ALC group					
		350@d30	18.5 (1.3–256)		NS			
Kumar S, 2001[26]	87 AML pts. BM only. Syngeneics and haplos excluded	Assessed measures: ALC@d21: 100, 150, 200 ALC@d30: 125, 150, 175, 200, 225	OS longer in high ALC group	RFS longer in high ALC group		RI lower in high ALC group		
		150@d30 with highest sig in RI	0.0047 UVar	0.0079 UVar		8.2 (2.2–30.1)		
Powles R, 1998[27]	201 AML pts. BM only. MA only. MRD only	d27,28,29,30 timepoints and ALC 100, 200, 300 cutoffs assessed	At 1 yr:					
		200@d29	25% vs. 65% (0.003)			2.9 (0.9–9.1)		

*Where percentages are given for OS, RFS, NRM, RI, and GVHD incidences, the first and second percentages indicate the survival/incidence in low and high absolute lymphocyte count groups, respectively

aGVHD: acute graft-versus-host disease, ALC: Absolute lymphocyte count, ALL: Acute lymphoid leukemia, AML: Acute myeloid leukemia, ATG: Anti-thymocyte globulin, BM: Bone marrow, b/o: based on, cGVHD: chronic graft-versus-host disease, CR: Complete remission, d: day, haplo: Haploidentical donor, HR: Hazard ratio, m: month, MA: Myeloablative, MDS: Myelodysplastic syndrome, MRD: Matched-related donor, MUD: Matched unrelated donor, NRM: Non-relapse mortality, NS: Not significant, OS: Overall survival PB: Peripheral blood, pts: patients, RFS: Relapse-free survival, RI: Relapse incidence, RIC: Reduced intensity conditioning, sig: significant, TBI: Total body irradiation, TCAB: T cell add-back, TCD: T cell depleted, UCB: Umbilical cord blood, UV: Univariate, yr: year

Table 2 -

Determination of optimal threshold for absolute lymphocyte count (ALC) for prediction of clinical outcomes

Measure	ALC Cutoff (/μL)	Training Set HR (95% CI)	Test Set HR (95% CI)	Bootstrap (Test Set) HR mean (95% CI)	Power
Overall survival					
ALC @ day 30	250	0.59 (0.45–0.78)	0.57 (0.37–0.89)	0.58 (0.34–0.90)	0.69
ALC @ day 60	300	0.42 (0.32–0.56)	0.43 (0.27–0.67)	0.43 (0.25–0.71)	0.93
ALC @ day 90	500	0.53 (0.39–0.71)	0.59 (0.37–0.93)	0.59 (0.35–0.91)	0.64
ALC @ day 120	420	0.50 (0.35–0.72)	0.36 (0.21–0.63)	0.38 (0.20–0.65)	0.93
ALC @ day 180	500	0.46 (0.30–0.72)	0.26 (0.11–0.59)	0.27 (0.01–0.63)	0.88
Relapse-free survival					
ALC @ day 30	250	0.61 (0.47–0.79)	0.57 (0.37–0.88)	0.58 (0.35–0.87)	0.72
ALC @ day 60	280	0.49 (0.37–0.66)	0.51 (0.33–0.79)	0.52 (0.30–0.83)	0.85
ALC @ day 90	500	0.57 (0.43–0.76)	0.57 (0.37–0.89)	0.57 (0.34–0.86)	0.73
ALC @ day 120	420	0.53 (0.37–0.75)	0.37 (0.22–0.64)	0.38 (0.21–0.64)	0.94
ALC @ day 180	500	0.47 (0.31–0.72)	0.22 (0.09–0.50)	0.23 (0.08–0.51)	0.93
Relapse					
ALC @ day 30	220	0.67 (0.47–0.94)	0.81 (0.43–1.54)	0.87 (0.45–1.55)	0.11
ALC @ day 180	750	0.55 (0.33–0.93)	0.67 (0.28–1.62)	0.76 (0.27–1.69)	0.16
Non-relapse mortality					
ALC @ day 30	250	0.50 (0.33–0.76)	0.27 (0.14–0.51)	0.28 (0.13–0.50)	0.98
ALC @ day 60	450	0.17 (0.10–0.29)	0.18 (0.09–0.38)	0.19 (0.07–0.36)	>0.99
ALC @ day 90	500	0.28 (0.17–0.46)	0.25 (0.12–0.53)	0.26 (0.10–0.50)	0.96
ALC @ day 120	415	0.38 (0.22–0.66)	0.18 (0.07–0.49)	0.20 (0.05–0.50)	0.94
ALC @ day 180	500	0.35 (0.18–0.70)	0.07 (0.01–0.40)	*	

HR: Hazard ratio

*Many of the bootstrapped samples for ALC on day 180 did not have non-relapse mortality events in one of the ALC groups, therefore, the results for this category were deemed questionable and not reported

Table 3 -

Primary causes of death according to absolute lymphocyte counts on post-transplant day 60 (ALC60)

Cause of death	ALC60 ≤300/μL (%) (N=102)	ALC60 >300/μL (N=173)
Recurrence/persistence of disease	41 (40)	126 (73)
Chronic GVHD	23 (23)	18 (10)
Acute GVHD	19 (19)	5 (3)
Infection	9 (9)	6 (3)
Organ failure	4 (4)	7 (4)
Graft rejection	1 (1)	4 (2)
Secondary malignancy	1 (1)	1 (1)
Hemorrhage	2 (2)	1 (1)
Other	2 (2)	5 (3)

Table 4 -

Multivariable analyses assessing the association between various patient-, disease-, and transplant-related factors and clinical outcomes

Measure	OS	RFS	RI	NRM	aGVHD*	cGVHD	CMV
Age (years)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.97, 1.00)	**1.02 (1.00, 1.04)**	0.99 (0.96, 1.02)	1.00 (0.98, 1.01)	0.99 (0.96, 1.02)
Diagnosis (AML/MDS vs. ALL)	0.84 (0.54, 1.32)	0.93 (0.60, 1.45)	0.83 (0.47, 1.44)	1.49 (0.65, 3.40)	0.78 (0.23, 2.72)	1.41 (0.82, 2.44)	0.59 (0.16, 2.18)
Matched donor (yes vs. no)	0.84 (0.61, 1.15)	0.80 (0.59, 1.10)	1.03 (0.69, 1.54)	**0.59 (0.37, 0.95)**	0.48 (0.19, 1.19)	0.86 (0.62, 1.21)	**0.40 (0.17, 0.96)**
Related donor (yes vs. no)	0.79 (0.54, 1.15)	0.72 (0.49, 1.05)	0.95 (0.56, 1.61)	0.60 (0.34, 1.07)	0.49 (0.17, 1.45)	0.74 (0.44, 1.24)	1.18 (0.39, 3.60)
CR at BMT (yes vs. no)	**0.38 (0.29, 0.50)**	**0.42 (0.32, 0.55)**	**0.37 (0.26, 0.52)**	0.91 (0.59, 1.39)	0.87 (0.41, 1.86)	0.97 (0.72, 1.30)	0.55 (0.25, 1.22)
Preparatory regimen (TBI vs. Other)	0.81 (0.49, 1.33)	0.89 (0.54, 1.46)	1.15 (0.59, 2.24)	0.95 (0.40, 2.26)	1.55 (0.26, 9.22)	1.03 (0.55, 1.92)	0.09 (0.00, 1.84)
Preparatory regimen (Busulfan vs. Other)	0.71 (0.54, 0.94)	0.69 (0.52, 0.91)	0.84 (0.59, 1.19)	0.68 (0.43, 1.08)	**3.45 (1.03, 11.56)**	0.87 (0.62, 1.23)	0.91 (0.39, 2.16)
ATG or alemtuzumab (yes vs. no)	0.79 (0.55, 1.14)	0.91 (0.63, 1.32)	1.40 (0.84, 2.33)	**0.54 (0.31, 0.95)**	0.46 (0.15, 1.42)	0.84 (0.51, 1.38)	1.74 (0.49, 6.18)
Post-BMT Cyclophos (yes vs. no)	0.82 (0.49, 1.39)	1.01 (0.61, 1.65)	1.27 (0.69, 2.32)	0.56 (0.23, 1.37)	2.01 (0.56, 7.21)	0.71 (0.38, 1.32)	1.34 (0.36, 4.98)
ALC60 group (>300 vs. ≤300/μL)	**0.46 (0.36, 0.60)**	**0.56 (0.43, 0.72)**	**1.68 (1.12, 2.51)**	**0.21 (0.14, 0.31)**	**0.37 (0.15, 0.92)**	0.79 (0.58, 1.08)	1.07 (0.46, 2.50)

aGVHD: acute graft-versus-host disease, ALC60: Absolute lymphocyte count on post-BMT day 60, ALL: Acute lymphoid leukemia, AML: Acute myeloid leukemia, ATG: Anti-thymocyte globulin, BMT: Bone marrow transplantation, cGVHD: chronic graft-versus-host diseae, CMV: Cytomegalovirus, CR: Complete remission, MDS: Myelodysplastic syndrome, NRM: Non-relapse mortality, OS: Oveall survival, RFS: Relapse-free survival, RI: Relapse incidence, TBI: Total body irradiation

*: aGVHD developed prior to day 60 were excluded from the analyses

Table 5 -

Comparison of clinical characteristics according to absolute lymphocyte count on post-bone marrow transplantation (BMT) day 60 (ALC60)

Measure	ALC60 ≤300/μL (N=134)	ALC60 >300/μL (N=353)	p-value
Age (years), median (range)	46 (18–71)	47 (18–71)	0.75
Diagnosis, n (%)			
AML/MDS	105 (78)	292 (83)	0.27
ALL	29 (22)	61 (17)	
Donor type, n (%)			
Matched unrelated	97 (72)	230 (65)	0.11
Mismatch unrelated	13 (10)	45 (13)	
Haploidentical	17 (13)	37 (10)	
Matched related	7 (5)	41 (12)	
Matched donor, n (%)			
Yes	104 (78)	271 (77)	0.84
No	30 (22)	82 (23)	
Related donor, n (%)			
Yes	24 (18)	78 (22)	0.31
No	110 (82)	275 (78)	
CR at BMT, n (%)			
Yes	63 (47)	185 (52)	0.29
No	71 (53)	168 (48)	
TBI-based conditioning, n (%)			
Yes	26 (19)	39 (11)	0.0155
No	108 (81)	314 (89)	
Busulfan-based conditioning, n (%)			
Yes	63 (47)	218 (62)	0.0033
No	71 (53)	135 (38)	
Conditioning intensity, n (%)			
Myeloablative	97 (72)	283 (80)	0.06
Reduced-intensity	37 (28)	70 (20)	
ATG or alemtuzumab, n (%)			
Yes	96 (72)	254 (72)	0.95
No	38 (28)	99 (28)	
Post-BMT cyclophosphamide, n (%)			
Yes	12 (9)	31 (9)	0.95
No	122 (91)	322 (91)	
Graft total nucleated cell count			
continuous, median(range)	2.42 (0.03 – 6.26)	2.67 (0.15 – 12.37)	0.13
≤ 2.59*, n (%)	73 (54)	171 (48)	0.23
> 2.59, n (%)	61 (46)	182 (52)	

Measure	ALC60 ≤300/μL (N=134)	ALC60 >300/μL (N=353)	p-value
Graft CD34+ cell count			
continuous, median(range)	2.99 (0 – 9.57)	3.12 (0 – 12.67)	0.24
≤ 3.03*, n (%)	73 (54)	171 (48)	0.23
> 3.03, n (%)	61 (46)	182 (52)	
Graft CD3+ cell count			
continuous, median(range)	18.79 (0 – 69.02)	21.16 (0 – 83.13)	0.20
≤ 20.43*, n (%)	75 (56)	166 (48)	0.10
> 20.43, n (%)	59 (44)	182 (52)	

ALL: Acute lymphoid leukemia, AML: Acute myeloid leukemia, ATG: Anti-thymocyte globulin, CR: Complete remission, MDS: Myelodysplastic syndrome, TBI: Total body irradiation