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Impact of Early Cytomegalovirus Reactivation in Cord Blood Stem Cell Recipients in the Current Era

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Abstract

Several studies have reported an association between cytomegalovirus (CMV) reactivation and a decreased incidence of relapse for acute myeloid leukemia (AML) after adult donor allogeneic

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hematopoietic cell transplantation (HCT). Limited data, however, are available on the impact of CMV reactivation on relapse after cord blood stem cell (CB) transplantation. The unique combination of higher incidence of CMV reactivation in the seropositive recipient and lower incidence of graft versus host disease (GvHD) in CB HCT allows for a valuable design to analyze the impact of CMV reactivation. Data from 1684 patients transplanted with cord blood (CB) between 2003 and 2010 for AML and acute lymphoblastic leukemia (ALL) were analyzed. The median time to CMV reactivation was 34 days (range: 2 – 287). CMV reactivation and positive CMV serology were associated with increased non-relapse mortality (NRM) amongst both AML and ALL CB recipients [Reactivation, AML: RR 1.41 (1.07–1.85); ALL: 1.60 (1.14 – 2.23); Serology, AML: RR 1.39 (1.05 – 1.85), ALL: RR 1.61 (1.18 – 2.19)]. For patients with ALL, but not those with AML, this yielded inferior overall survival ($p < 0.005$). Risk of relapse was not impacted by CMV reactivation or positive CMV serostatus for either disease.

Keywords

Cytomegalovirus; umbilical cord blood; allogeneic transplant; leukemia

INTRODUCTION

Since the early years of transplant, a positive CMV serology in the recipient, and CMV reactivation have been associated with inferior outcomes after HCT, reflecting an increase in non-relapse mortality (NRM)¹. However, the development and adoption of effective monitoring of CMV either by polymerase chain reaction (PCR) or pp65 antigenemia (pp65-AG) in the blood, and the use of pre-emptive antiviral therapy in the late 1990s/early 2000, has had a favorable impact on reducing the incidence of CMV disease and resulted in a decline in CMV-associated mortality².

Recently, some studies have reported an association of positive CMV serology or early (before day 100) CMV reactivation with decreased incidence of relapse after HCT^{3–8}. This protective effect against relapse appears restricted to AML, and, in some single center studies, is associated with an improvement in overall survival^{3–5, 8}. One hypothesis is that CMV reactivation results in expansion of natural killer (NK) cells with a mature phenotype (CD56^{dim}, NKG2C⁺ and CD57⁺) that produce INF γ ⁹. Mature NK cell expansion is hypothesized to enhance antitumor responses, providing a biological rationale for reduced relapse occurring after CMV reactivation. T cells may be also involved since some $\gamma\delta$ T cells recognize CMV peptides that are cross reactive against leukemia cells¹⁰. Consistent with this hypothesis, use of anti-thymocyte globulin or alemtuzumab (serotherapy) has been reported to abrogate the benefit of CMV reactivation on relapse^{11–15}. Published literature is conflicting as several studies have failed to show a favorable association between CMV serology or reactivation and leukemia relapse or survival^{4, 5, 7, 8, 14, 16–18}.

None of these prior studies focused on the impact of CMV recipient serostatus or CMV reactivation in cord blood (CB) recipients. It is critical to look at CMV reactivation outcomes in CBHCT specifically as CBHCT is unique. CB T cells are naïve and there is no transfer of protective memory T cells¹⁹; therefore, CB is considered inherently seronegative

and CB transplant is associated with a high incidence of CMV reactivation in the seropositive recipient. CBHCT also tends to be associated with less acute and chronic GVHD given the degree of mismatch, yet a powerful graft versus leukemia effect remains^{20–22}.

Given the disparity in the medical literature for the influence of CMV on leukemia relapse, and lack of sufficient CB data, the primary aim of this study was to use the large multi-institutional database of the CIBMTR to more completely analyze the impact of cord blood recipient serostatus and early CMV reactivation primarily on leukemia relapse; secondary outcomes included the impact on overall survival (OS), and non-relapse mortality (NRM), in the era of preemptive therapy.

PATIENTS AND METHODS

Data source

The CIBMTR is a working group of more than 500 transplant centers worldwide that provide detailed patient, disease, transplant characteristics and outcomes of consecutive transplantations. Data are collected at the Statistical Center at the Medical College of Wisconsin or at the Data-Coordinating Center of the National Marrow Donor Program, where computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. The CIBMTR collects both Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data before transplantation, 100 days (D100) and 6 months after transplantation, and annually thereafter. All subjects whose data were included in this study provided institutional review board-approved consent to participate in the CIBMTR Research Database and have their data included in observational research studies. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Data collection and criteria for selection

All patients reported to the CIBMTR, and receiving first CBHCT between 2003 and 2010, for AML and ALL using any conditioning regimen, were included. Patients with only former National Marrow Donor Program (NMDP) forms were excluded given lack of data on CMV reactivation (n = 298). Patients from centers with less than 30% completeness of follow-up index were also excluded (n = 64). Other exclusion criteria were: no signed informed consent (n = 35), lack of day100 follow-up forms capturing CMV reactivation data (n = 70), CMV serostatus match missing and death before transplantation (n=4). A total of 1684 cord blood recipients with AML and ALL are included in this analysis. The database was locked on August 31, 2013. The completeness index was very good, 99% at 1 year and 97% at 5 years of follow-up.

Data regarding CMV reactivation, surveillance and treatment

The CIBMTR day 100 follow-up forms collect information on the date of onset of CMV reactivation and the site where CMV was identified. There is no information collected regarding diagnostic method, level of virus detected, nor information on therapy provided.

Study design and Statistical analysis

Patients with AML (n = 925) and ALL (n = 759) were analyzed separately. For univariate outcomes and the initial multivariable analysis, patients were categorized as D-/R+ or D-/R-, since CB is considered inherently CMV seronegative. A second multivariable analysis was performed based on the presence or absence of CMV reactivation post-transplant as a time-dependent covariate. Patients receiving single (n = 944) and double (n = 740) cord were analyzed together since randomized trials demonstrate no difference in transplant outcomes of relapse and survival with single versus double cord transplant²³.

Variables included time to CMV reactivation, CMV (D/R) serology, recipient age, gender, race, Karnofsky score at HCT, time from diagnosis to HCT, disease risk category based on ASBMT RFI 2014 classification²⁴, year of transplant (2003–2006 vs 2007–2010), conditioning intensity, use of total body irradiation (TBI), use of serotherapy, Graft versus Host Disease (GVHD) prophylaxis regimen, and development of acute and/or chronic GVHD post-transplant. For multivariable analyses, the main effect variable was either D/R CMV serology (D-/R- as reference vs. D-/R+) or CMV reactivation as a time dependent covariate (yes vs. no). Additional variables analyzed in the models included age (< 10 years vs. 10–30y vs. > 30y), disease risk category, conditioning intensity, serotherapy (Yes vs. No), GVHD prophylaxis (Tacrolimus/Cyclosporine + Methotrexate ± Others vs. Tacrolimus/Cyclosporine + Others vs. Others) and acute GVHD (aGVHD) occurring prior to CMV reactivation as a time dependent covariate.

Patient, disease and transplant-related factors were compared between groups using the Pearson chi-square test for discrete variables and the Kruskal-Wallis test for continuous variables. Probabilities of disease-free and overall survival were calculated using the Kaplan Meier estimator. Values for other endpoints were generated using cumulative incidence estimates to account for competing risks. Overall survival (OS) was defined as the time to death from any cause with surviving patients censored at time of last follow-up. Disease free survival (DFS) was defined as the time to relapse or death from any cause. Non relapse mortality (NRM) was defined as death without evidence of disease with relapse as a competing risk. Relapse was recurrence/progression of acute leukemia with death as the competing risk. For aGVHD grade II–IV and chronic GVHD (cGVHD) of any severity, death was the competing risk and patients were censored at time of relapse. In both multivariable analyses of CMV serology and CMV reactivation, the proportional hazard assumption was examined. If violated, it was included as a time-dependent covariate. A stepwise selection procedure was used. Interactions between the main effect and significant covariates were examined. A p-value <0.05 was considered significant. SAS v9.3 (Cary, NC) was used for statistical analysis.

RESULTS

Distribution of CMV serology and CMV reactivation

Table 1 provides basic information on the patients included in the analysis. A total of 1011 CB recipients were CMV serostatus positive with 606 (66%) in the AML cohort and 405 (53%) in the ALL cohort reflecting the older median age for patients with AML [ALL,

median 12 (<1 – 68) years vs AML, 28 (<1 – 79) years; $p < 0.001$]. The median time to CMV reactivation for the entire cohort was 34 days (range, 2 – 287) after HCT. It was similar for the AML cohort regardless of D/R serostatus; however, for ALL patients, the 4% of D–/R– who developed reactivation occurred significantly later after transplant. Nearly all CMV reactivations occurred in the first 3 months after transplant.

Relapse

For patients with AML, relapse by 1 year occurred in 27% (95% Confidence interval [CI], 23 – 31%) of seropositive recipients and 26% (95% CI, 21 – 31%) of seronegative recipients ($p = 0.77$) (Table 2 and figure 1A). Relapse at 1 year was slightly lower in patients with ALL but there was no effect of recipient CMV serostatus [D–/R+, 20% (95% CI, 16 – 24%); D–/R–, 18% (95% CI, 14 – 22%), $p = 0.49$] (Table 2 and figure 1B).

In multivariable analysis adjusted for other known risk factors for relapse, CMV seropositive recipients with AML had a higher risk of relapse (RR 1.39, $p = 0.022$) compared to seronegative recipients (Table 3). For ALL patients, the risk of relapse was slightly higher for the CMV seropositive recipients, albeit not statistically significant, (Table 4). CMV reactivation as a time dependent event did not favorably impact relapse for patients with either AML or ALL [AML: RR 0.8 (95% CI, 0.62 – 1.04), $p = 0.097$; ALL: RR 1.01 (95% CI, 0.70 – 1.46), $p = 0.95$]. As expected, AML and ALL patients with high-risk disease or recipients of reduced intensity conditioning had a higher risk of relapse. ALL patients developing acute GVHD were less likely to have disease relapse [RR of 0.7 (95% CI, 0.52 – 0.94), $p < 0.02$].

Graft vs Host Disease

Acute GVHD grade II – IV by day 100 was similar regardless of disease indication for transplant or CMV recipient serostatus [AML D–/R+: 43% (95% CI, 39 – 47%); AML D–/R–: 40% (95% CI, 34 – 45%); ALL D–/R+: 39% (95% CI, 34 – 44%); ALL D–/R–: 40% (95% CI, 35 – 45%)]. Chronic GVHD by 3 years did not differ [AML D–/R+: 30% (95% CI, 26 – 33%); AML D–/R–: 34% (95% CI, 28 – 39%); ALL D–/R+: 31% (95% CI, 27 – 36%); ALL D–/R–: 35% (95% CI, 30 – 40%)]

In multivariable analysis, positive CMV serology had no impact on the incidence of aGVHD or cGVHD in AML or ALL. CMV reactivation occurring prior to the onset of acute GVHD demonstrated a slightly increased but not statistically different risk of aGVHD [AML: RR 1.31 (95% CI, 0.96 – 1.79), $p = 0.083$; ALL: RR 1.38 (95% CI, 0.96 – 1.98), $p = 0.084$]. CMV reactivation had no impact on the development of cGVHD when adjusted for other factors.

Other factors impacting development of aGVHD grade II – IV included the use of serotherapy for either disease; although for patients with AML, this effect became attenuated after 1 month post-transplant (Table 3). There was also a decreased risk of aGVHD for patients with AML receiving a RIC regimen but this only occurred in the first month from transplant. As expected, chronic GVHD was decreased in patients receiving serotherapy, regardless of underlying malignancy (Table 3). Additionally, for patients with ALL, older age and prior aGVHD increased the risk for development of cGVHD (Table 4).

Non-relapse mortality (NRM)

Recipient CMV serology and CMV reactivation were both associated with increased NRM. In univariate analysis, patients with AML who were D–/R+ had an increased risk of NRM at 1 year and 3 years compared to D–/R– pairs [1 year, D–/R+: 26% (95% CI, 23 – 30%) vs D–/R–: 18% (95% CI, 14 – 22%), $p = 0.003$; Table 2, Figure 2A]. This was similar in patients with ALL as well (Table 2, Figure 2B). This effect remained significant for both AML and ALL when adjusted for other factors in multivariable analysis (Table 3, Table 4). Similarly, CMV reactivation increased NRM in multivariable analysis such that patients with AML had a 1.4-fold greater risk (95% CI, 1.07 – 1.85; $p < 0.02$) and those with ALL were about 1.6-times as likely to die of NRM (95% CI, 1.14 – 2.23; $p > 0.007$).

For patients with AML, older age was also associated with increased NRM. For ALL, increased age, use of serotherapy, and the development of aGVHD were all associated with increased NRM.

Survival

As shown in Table 2, both disease free (DFS) and overall (OS) survival were inferior for patients with acute leukemia who were CMV seropositive (Figure 3A, 3B). When adjusting for other factors, this effect was no longer significant in AML patients (Table 3). However, for ALL patients, CMV seropositive recipients had a higher risk of death from any cause (Table 4). Use of serotherapy adversely impacted DFS. For ALL patients not receiving serotherapy, DFS was similar to CMV seronegative recipients; however, the use of serotherapy was associated with significantly inferior DFS in CMV seropositive recipients.

When adjusting for CMV reactivation, there was no impact on DFS or OS for patients with AML [DFS, RR 1.05 (95% CI, 0.87 – 1.27), $p = 0.61$; OS: RR 1.07 (95% CI, 0.88 – 1.30), $p = 0.48$]; however, patients with ALL and a CMV reactivation had inferior DFS [RR 1.31 (95% CI, 1.02 – 1.67), $p = 0.03$] and higher risk of death [RR 1.44 (95% CI, 1.12 – 1.84), $p < 0.005$].

Regardless of type of acute leukemia, patients with more advanced disease and older age had a higher risk of death and impaired DFS. For patients with ALL, patients receiving reduced intensity conditioning had inferior DFS and OS. Specific causes of death for all patients by D/R serostatus are shown in Table 5.

DISCUSSION

Several studies have examined the impact of CMV reactivation specifically in AML after HCT. However, none of these studies examined outcomes in the CB setting. This CIBMTR analysis of 1684 patients was specifically designed to look at the influence of CMV serology and early CMV reactivation on relapse and survival following cord blood HCT for either AML or ALL. Our data suggest that CMV reactivation does not prevent relapse of AML or ALL in patients receiving CB HCT. Furthermore, our study highlights a persistent negative impact for CB recipients who are CMV seropositive and for patients experiencing CMV reactivation after CB HCT.

The lack of benefit of CMV seropositivity and CMV reactivation seen in our analysis contrasts with other studies which have described a protective effect for positive CMV serology or CMV reactivation in preventing AML relapse^{4, 5, 7, 8, 17, 25}. However, other studies have reported a lack of benefit from positive CMV serology and a negative effect of early CMV reactivation with regards to the risk of leukemia relapse^{18, 26}. A recent analysis from the European Blood and Marrow Transplant Group (EBMT) demonstrated a higher risk of leukemia relapse and poorer overall survival associated with positive CMV serology^{17, 27}.

CMV reactivation and positive CMV serology (D-/R+ vs. D-/R-) increased NRM in our cohort. Similar to the EBMT study, we found that CMV seropositive recipients were more likely to have infection reported as a primary cause of death compared to CMV seronegative CB recipients (R+, 21%; R-, 14%). Notably, there was a roughly similar increase in recurrence/persistent disease as the primary cause of death in CMV seronegative recipients (R+, 37%; R-, 48%). Despite these findings, there was no protection from relapse seen in either univariate or multivariable analysis. Since an indirect effect of CMV serology on the risk of infections with other pathogens has been reported, it is possible that any small decrease in relapse risk is counter-balanced by an increase in fatal infections²⁸.

For patients with ALL who received either ATG or alemtuzumab serotherapy, CMV reactivation and a positive CMV recipient serology was detrimental to LFS. Influence of serotherapy on LFS may be explained by the higher likelihood of CMV reactivation in these patients¹². CMV positive serology (p=0.0007) and CMV reactivation (p=0.0042) had a negative impact on OS in ALL. This negative impact in ALL is not surprising given the negative impact on both NRM and LFS in ALL CB recipients. Notably, CMV status (positive serology or CMV reactivation) had no impact on LFS or OS in AML. It is interesting that despite its negative impact on NRM, CMV status did not negatively impact OS in AML CB. The differences in outcomes between AML and ALL cannot be solely attributed to disease category as non-disease related factors such as age and prior chemotherapy may have played a role as well. Within the ALL group, predominantly younger patients, recipient CMV seropositivity was a stronger predictor of NRM compared to AML patients which may account for the lack of impact of CMV status on LFS and OS for AML patients.

While multicenter registry studies such as ours have the advantage of a large sample size, the caveat is the lack of detailed information. Data with regards to the viral monitoring test used to diagnose CMV reactivation, frequency of testing or preemptive versus prophylactic policies applied by each center were not available. In addition, information regarding antiviral therapy itself, trigger for initiation, timing of initiation and total duration of treatment for CMV reactivation were not captured. Moreover, CMV reactivation may be under-reported in multicenter registry studies. This is likely explained by a trend for reporting to registries only CMV reactivations which are considered to have a clinical importance due to their level or duration. The lack of detailed data may introduce bias diluting the effect of CMV serostatus and CMV reactivation; however, the large number of patients and centers should counter this bias somewhat.

The implications of our CB study showing the persistent negative impact of CMV serostatus and reactivation on NRM despite the existence of effective antiviral pharmacotherapy are far-reaching. Although antiviral pharmacotherapy, diligent surveillance and early pre-emptive anti-viral therapy has significantly reduced the progression to CMV disease and mortality observed prior to this era, there remains significant limitations to current therapy including myelosuppression (ganciclovir) and electrolyte imbalances/renal impairment (foscarnet). Our data justifies the need for development of novel antiviral drugs, with superior efficacy and toxicity profiles^{29, 30}. For example, a prophylactic rather than pre-emptive approach may lead to superior outcomes in CB stem cell transplants. Some centers have reported using IV ganciclovir during conditioning regimen (day -8 to -2) and high dose valacyclovir prophylaxis (2gm every 8 hours) in the post-transplant setting in their CMV seropositive CB recipients. An alternative approach to antiviral pharmacotherapy, especially in CBHCT, is adoptive cellular immunotherapy for CMV and other viral diseases^{31, 32}. Adoptive cellular immunotherapy, after having amassed an excellent record for efficacy and safety, is advancing from therapy of refractory disease to prophylaxis. Boosting immune reconstitution and antiviral immunity post (CB) HCT rather than focusing on pharmacotherapy has the potential to be cost effective³³⁻³⁵. Regardless of the approach, our data confirms that there is a great scope for further improving the management of CMV after cord blood HCT.

In conclusion, in this only multicenter dataset of cord blood recipients, CMV reactivation is associated with decreased DFS and OS in ALL but not in AML. Positive recipient CMV serology and CMV reactivation continues to contribute to increased NRM even in the era of pre-emptive treatment. If CMV reactivation has an effect on decreasing AML relapse, our study suggests that the benefit is small and likely balanced by the increased NRM, particularly in the setting of CBHCT.

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A: AML **B. ALL** **Figure 1.**

Cumulative incidence curves of relapse for patients with AML (A) and ALL (B) based upon the CMV serostatus of the recipient

A. AML **B. ALL** **Figure 2.**

Cumulative incidence curves of NRM for patients with AML (A) and ALL (B) based upon the CMV serostatus of the recipient

A. AML **B. ALL** **Figure 3.**

Overall Survival for patients with AML (A) and ALL (B) based upon CMV serostatus of the recipient.

Table 1

Variable	AML			ALL		
	D-/R+ N (%)	D-/R- N (%)	p-value	D-/R+ N (%)	D-/R- N (%)	p-value
Number of patients	606	319		405	354	
Number of Centers	125	105		117	90	
Age, median (range), years	28 (<1 – 79)	19 (<1 – 77)	0.002	12 (<1 – 68)	8 (<1 – 68)	<0.001
Gender, male	267 (44%)	180 (56%)	<0.001	243 (60%)	217 (61%)	0.715
KPS at transplant						
90%	430 (71%)	244 (76%)	0.088	296 (73%)	266 (75%)	0.390
< 90%	162 (27%)	65 (20%)		99 (24%)	75 (21%)	
Missing	14 (2%)	10 (3%)		10 (2%)	13 (4%)	
Time from diagnosis to HCT, months median (range)	8 (<1–293)	7 (<1–313)	0.025	16 (<1–144)	21 (3–169)	0.144
Disease risk at transplant						
Low	241 (40%)	152 (48%)	0.033	148 (37%)	122 (34%)	0.517
Intermediate	227 (37%)	112 (35%)		228 (56%)	212 (60%)	
High	138 (23%)	54 (17%)		29 (7%)	20 (6%)	
Conditioning intensity						
MAC	441 (73%)	239 (75%)	0.616	362 (89%)	322 (91%)	0.467
RIC/NMA	164 (27%)	80 (25%)		43 (11%)	32 (9%)	
CMV reactivation in blood by 1 year after HCT, yes	249 (41%)	18 (6%)	<0.001	151 (37%)	14 (4%)	<0.001
Follow-up of survivors, months median (range)	48 (3 – 116)	48 (4 – 121)		47 (6–103)	55 (4–127)	

* abbreviations: KPS = Karnofsky performance status; MAC = myeloablative conditioning, RIC = reduced intensity conditioning, NMA = non-myeloablative conditioning

Table 2

Univariate analysis for 3-year outcomes according to CMV serologic status of the donor and recipient

Disease	D-/R+ % (95% CI)	D-/R- % (95% CI)	p-value
RELAPSE			
AML	35% (31 – 38%)	35% (29 – 40%)	0.99
ALL	28% (23 – 32%)	24% (20 – 29%)	0.30
NON-RELAPSE MORTALITY			
AML	29% (26 – 33%)	20% (16 – 25%)	0.002
ALL	29% (24 – 33%)	18% (14 – 23%)	<0.001
OVERALL SURVIVAL			
AML	38% (34 – 42%)	47% (41 – 52%)	0.01
ALL	46% (42 – 51%)	62% (57 – 67%)	<0.001
DISEASE FREE SURVIVAL			
AML	36% (32 – 40%)	45% (40 – 51%)	0.009
ALL	43% (38 – 48%)	57% (52 – 62%)	<0.001

Table 3

Multivariable outcomes for patients with AML receiving CB transplant

Variable*	Relative Risk (95% CI)	p- value
Acute GVHD		
CMV D-/R+	1.116 (0.904 – 1.378)	0.3085
RIC		
1mo post HCT	0.566 (0.407 – 0.786)	0.0007
> 1 mo post HCT	1.082 (0.778 – 1.505)	0.6389
ATG/CAMPATH, yes		
1mo post HCT	0.425 (0.317 – 0.568)	<0.0001
> 1 mo post HCT	0.866 (0.639 – 1.174)	0.355
Chronic GVHD		
CMV D-/R+	0.921 (0.722 – 1.176)	0.5105
ATG/CAMPATH, yes	0.572 (0.447 – 0.732)	<0.0001
Relapse		
CMV D-/R+	1.395 (1.049 – 1.855)	0.022
Disease Risk		<0.0001 (overall)
Intermediate [‡]	1.239 (0.948 – 1.619)	0.1163
High	3.324 (2.519 – 4.387)	<0.0001
RIC	2.055 (1.625 – 2.598)	<0.0001
Non-Relapse Mortality		
CMV D-/R+	1.395 (1.049 – 1.855)	0.022
Age		<0.0001 (overall)
11 – 30 years [‡]	1.877 (1.286 – 2.74)	0.0011
>30 years	2.074 (1.462 – 2.941)	<0.0001
Disease Free Survival		
CMV D-/R+	1.16 (0.969 – 1.388)	0.1053
Age		<0.0001 (overall)
11 – 30 years [‡]	1.198 (0.943 – 1.520)	0.1384
>30 years	1.633 (1.326 – 2.011)	<0.001
Disease Risk		<0.0001 (overall)
Intermediate [‡]	0.998 (0.822 – 1.211)	0.983
High	1.779 (1.441 – 2.196)	<0.0001

Variable*	Relative Risk (95% CI)	p- value
Overall Survival		
CMV D-/R+	1.184 (0.988 – 1.42)	0.0667
Age		<0.0001 (overall)
11 – 30 years [‡]	1.259 (0.991 – 1.599)	0.0594
>30 years	1.599 (1.295 – 1.973)	<0.0001
Disease Risk		<0.0001 (overall)
Intermediate [‡]	0.962 (0.789 – 1.172)	0.6999
High	1.880 (1.527 – 2.314)	<0.0001

* Reference groups: CMV D-/R-; Myeloablative conditioning; ATG/CAMPATH, no; Disease risk, low; Age = 10 years

[‡] Disease risk Int vs High: Relapse 0.3727 (0.2842 – 0.4889), p < 0.0001; DFS 0.561 (0.4511 – 0.6976), p < 0.0001; OS 0.5117 (0.4122 – 0.6353), p < 0.0001

[‡] Age 11 – 30 vs > 30 years: NRM 0.9052 (0.6781 – 1.2086), p = 0.4995; DFS 0.7333 (0.5987 – 0.8991), p 0.0027; OS 0.7872 (0.6429 – 0.9640), p = 0.0206

Table 4

Multivariable outcomes for patients with ALL receiving CB transplant

Variable*	Relative Risk (95% CI)	p- value
Acute GVHD		
CMV D-/R+	0.885 (0.705 – 1.113)	0.2964
ATG/CAMPATH, yes	0.458 (0.359 – 0.584)	<0.0001
GVHD Prophylaxis		0.0463 (overall)
TAC/CSA + others (no MTX)//	1.483 (1.052 – 2.09)	0.0245
Others	0.833 (0.297 – 2.334)	0.7275
Chronic GVHD		
CMV D-/R+	0.912 (0.705 – 1.179)	0.4806
Age		0.0227 (overall)
11 – 30 years [‡]	1.25 (0.938 – 1.664)	0.1273
>30 years	1.635 (1.114 – 2.336)	0.0069
ATG/CAMPATH, yes	0.686 (0.517 – 0.909)	0.0088
Acute GVHD, yes	2.172 (1.668 – 2.829)	< 0.0001
Relapse		
CMV D-/R+	1.3 (0.982 – 1.72)	0.067
Disease Risk (≤ 6 mos from HCT)		< 0.0001 (overall)
Intermediate [‡]	2.064 (1.211 – 3.518)	0.0077
High	10.576 (5.618 – 19.908)	< 0.0001
Disease Risk (> 6 mos from HCT)		0.0015 (overall)
Intermediate [‡]	2.241 (1.438 – 3.492)	0.0004
High	2.506 (0.870 – 7.213)	0.0886
RIC	3.132 (2.188 – 4.485)	<0.0001
Acute GVHD, yes	0.70 (0.519 – 0.944)	0.0192
Non-Relapse Mortality		
CMV D-/R+	1.608 (1.178 – 2.193)	0.0027
Age (≤ 6 mos from HCT)		<0.0001 (overall)
11 – 30 years [‡]	1.45 (0.959 – 2.192)	0.0779
>30 years	2.555 (1.607 – 4.065)	<0.0001
Age (> 6 mos from HCT)		<0.0001 (overall)

Variable*	Relative Risk (95% CI)	p- value
11 – 30 years [‡]	1.784 (0.961 – 3.309)	0.0664
>30 years	4.9 (2.541 – 9.449)	<0.0001
ATG/CAMPATH, yes	1.808 (1.321 – 2.472)	0.0002
Acute GVHD, yes	1.535 (1.127 – 2.091)	0.0065
Disease Free Survival		
CMV D–/R+ and ATG/CAMPATH no	1.0359 (0.7803 – 1.3752)	0.8072
CMV D–/R+ and ATG/CAMPATH yes	1.9745 (1.4636 – 2.6638)	<0.0001
Age		< 0.0001 (overall)
11 – 30 years [‡]	1.298 (1.03 – 1.635)	0.0272
>30 years	2.085 (1.543 – 2.817)	<0.0001
Disease Risk (≤ 6 mos from HCT)		<0.0001 (overall)
Intermediate [‡]	1.497 (1.0999 – 2.04)	0.0105
High	3.43 (2.178 – 5.401)	<0.0001
Disease Risk (> 6 mos from HCT)		< 0.0001 (overall)
Intermediate [‡]	1.747 (1.244 – 2.453)	0.0013
High	2.045 (0.966 – 4.331)	0.0617
RIC	1.733 (1.285 – 2.337)	0.0003
Overall Survival		
CMV D–/R+	1.462 (1.175 – 1.8181)	0.0007
Age		0.0003 (overall)
11 – 30 years [‡]	1.332 (1.049 – 1.693)	0.0186
>30 years	1.903 (1.387 – 2.612)	<0.0001
Disease Risk		<0.0001 (overall)
Intermediate [‡]	1.584 (1.24 – 2.022)	0.0002
High	3.548 (2.438 – 5.165)	<0.0001
RIC	1.556 (1.134 – 2.134)	0.0061
ATG/CAMPATH, yes	1.278 (1.03 – 1.585)	0.0257

* Reference groups: CMV D–/R–; ATG/CAMPATH, no; GVHD prophylaxis TAC/CSA + MTX, Acute GVHD, no; Disease risk, low; Age 10 years

// GVHD prophylaxis TAC/CSA + Others vs Others: aGVHD 1.781 (0.6632 – 4.7829), p = 0.2521

[‡] Disease risk Int vs High: Relapse ≤ 6 months 0.1952 (0.1176 – 0.324), p < 0.0001; > 6 months 0.8943 (0.3262 – 2.4516), p = 0.8281; DFS ≤ 6 months 0.4366 (0.2846 – 0.6696), p = 0.0001; >6 months 0.8543 (0.4107 – 1.7773), p = 0.6736; OS 0.7001 (0.514 – 0.9536), p 0.0237

‡ Age 11 – 30 vs > 30 years: cGVHD 0.7643 (0.5321 – 1.0977), $p = 0.1456$; NRM 6 months 0.5675 (0.358 – 0.8996), $p = 0.0159$; > 6 months 0.3641 (0.1927 – 0.6877), $p = 0.0018$; DFS 0.6225 (0.4619 – 0.839), $p = 0.0019$; OS 0.4463 (0.3117 – 0.639), $p < 0.0001$

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Table 5

Causes of death for patients with AML or ALL undergoing CB HCT based on donor and recipient (D/R) CMV serostatus. Overall, there is no difference in the primary cause of death reported ($p = 0.18$).

Cause of Death	D-/R+ N (%)	D-/R- N (%)
Recurrent/Persistent Leukemia	223 (37%)	151 (48%)
Infection	126 (21%)	45 (14%)
Organ failure	109 (18%)	56 (18%)
GVHD	36 (6%)	16 (5%)
Graft rejection	19 (3%)	10 (3%)
Other *	71 (12%)	35 (11%)
Unknown	14 (2%)	4 (1%)

* Other causes include interstitial pneumonitis (n = 7), Hemorrhage (n = 38), Second malignancy (n = 7), and other unspecified causes (n = 54)