Donor cytomegalovirus serology impacts overall survival in children receiving first unrelated hematopoietic stem cell transplant for acute leukemia: European Society of Bone Marrow Transplantation Pediatric Diseases Working Party Study

Despite the universal implementation of DNA-based screening and pre-emptive antiviral treatment, cytomegalovirus (CMV) infection remains a significant risk factor for morbidity and mortality in allogeneic hematopoietic stem cell transplantation (HSCT).[1-5] Patient CMV seropositivity prior to HSCT has consistently been associated with increased risk of CMV reactivation and CMV disease.[2,6] Of note, overall survival (OS) remains inferior in CMV seropositive recipients (R+) irrespective of CMV disease,[7,8] suggesting that CMV mediates its detrimental impact not only via direct cytopathic effects but also through indirect effects related to viral replication and use of antiviral therapy on number and functionality of hematopoietic and immune cells. Previously published adult-focused registry analyses have shown that impact of patient's CMV serostatus on outcome may be mitigated by selecting donors displaying "compatible" CMV serostatus with selecting negative donors for negative patients providing more pronounced benefit.[1,5] Based on paucity of such data in the setting of pediatric HSCT for acute leukemia (AL), the most frequent transplantation indication for children, we investigated the impact of CMV serostatus of donors and recipients in a large pediatric HSCT cohort homogeneously treated in the contemporary era and reported to the EBMT.

This is a retrospective study of pseudonymized clinical data reported to the European Society for Blood and Marrow Transplantation (EBMT) registry. The study was approved by the Pediatric Diseases Working Party (PDWP) of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki. Children (age <18 years) with acute myeloid (AML) or lymphoblastic leukemia (ALL) receiving the first allogeneic HSCT between 2005 and 2021 were included. All patients received a bone marrow (BM) or peripheral blood (PB) transplant from an HLA-matched unrelated donor (10/10 at loci A, B, C, DRB1 and DQB1 in high resolution) uniformly. Transplant procedures using *in vivo* T-cell depletion (ATG or alemtuzumab) were included. Cord-blood transplantation, transplant procedures involving *ex vivo* T-cell depletion or PTCy were excluded. The primary objective was to assess the impact of donor CMV serology on OS in pediatric HSCT recipients with AML or ALL. The secondary objectives were the comparison of leukemia-free survival (LFS), non-relapse mortality (NRM), relapse incidence (RI), incidence of both acute graft-*versus*-host disease (aGvHD) and chronic GvHD (cGvHD), and GvHD-free/relapse-free survival (GRFS) between the seropositive (D+) and seronegative (D-) donor groups. Based on prior identification of substantial interaction between donor and recipient CMV serology in adult studies,[1] all analyses were performed in two separate cohorts: CMV seropositive (R+) and CMV seronegative (R-) pediatric HSCT recipients. Quantitative variables were described as median, interquartile range (IQR [quartiles 1 and 3]), minimum, and maximum. Differences between quantitative variables and donor CMV seropositivity were tested using Wilcoxon tests. Qualitative variables are described as numbers and percentages. Differences between qualitative variables and donor CMV seropositivity were tested using χ^2 tests or exact Fisher tests. OS, LFS, and GRFS were estimated using the Kaplan-Meier estimator. Variables with competing events were estimated using the cumulative incidence function. Median follow-up was estimated using the reverse Kaplan-Meier estimator. The impact of donor CMV serology was estimated and tested using Cox models. Adjusting factors, which were selected according to their potential impact on survival, were source of cells (BM or PB), indicator of female donor to male recipient, Disease Risk Index (DRI) as two categories (low/intermediate *vs*. high/very high) [vhigh], use of total body irradiation (TBI), patient age at transplant, donor age at transplant, and year of transplant. The DRI was calculated as defined by Armand *et al*.[9] and using for the AML the cytogenetic classification of the European Leukemia Net 2017.[10] The center effect was considered frailty. Punctual estimation of the outcomes and hazard ratio (HR) were given with their 95% confidence interval (CI). Two-sided *P* values <0.05 were considered statistically significant. Analyses were performed using the statistical R software version 4.0.2.

In total, 1,640 AL patients (R+: 909; R-: 731) with a median age of 8.9 years (IQR, 0.3-18 years) were analyzed. Patient, disease and transplant characteristics and transplant outcomes are summarized in *Online Supplementary Tables S1* and *S2*, respectively.

In R+ patients, those receiving HSCT from a seropositive donor (R+/D+) had a significantly better OS (2-year OS: 79% *vs*. 69%, HR=0.66; *P*=0.002) (Figure 1A), better LFS (2-year LFS: 70% *vs*. 63%, HR=0.75; *P*=0.01) and lower NRM (2-year 7% *vs*.

13%, HR=0.52; *P*=0.004) compared to children transplanted from a seronegative donor (R+/D-) in Cox multivariable analyses. Donor CMV serology showed no significant association with RI, aGvHD, cGvHD or GRFS. Use of TBI (HR=0.70; *P*=0.01) and HSCT in more recent years (HR=0.79; *P*=0.01) correlated significantly with improved OS, whereas high/vhigh DRI was associated with worse OS (HR=1.57; *P*<0.001) (Table 1).

In contrast, in R- patients, donor CMV serology had no significant association with OS (Figure 1B) (2-year OS: 79% *vs.* 76%, HR=1.13; *P*=0.47), LFS (2-year LFS: 70% *vs.* 65%, HR=1.15; *P*=0.35), RI (2-year LFS: 24% *vs.* 24%, HR=1.04; *P*=0.82) or NRM (2-year NRM: 7% *vs.* 11%, HR=1.53; *P*=0.14) in D- and D+, respectively in Cox multivariable analysis. The only factor independently associated with OS was increasing patient age (HR=1.17; *P*<0.001) (Table 1).

In total, 237 of 909 patients in R+ group and 181 of 731 pa-

Table 1. Association of donor cytomegalovirus serology with transplant outcomes in multivariable Cox regression analysis.

Parameter	OS HR (95% CI) *P*	LFS HR (95% CI) *P*	NRM HR (95% CI) *P*	RI HR (95% CI) *P*	aGvHD II-IV HR (95% CI) *P*	cGvHD HR (95% CI) *P*	GRFS HR (95% CI) *P*
CMV seropositive patients							
Donor CMV: - *vs.* +	0.66 (0.51-0.86) 0.002	0.75 (0.59-0.94) 0.01	0.52 (0.34-0.81) 0.004	0.86 (0.66-1.13) 0.28	0.97 (0.61-1.56) 0.68	1.06 (0.72-1.56) 0.76	0.83 (0.68-1.03) 0.09
Source of cells: BM *vs.* PB	1.20 (0.90-1.58) 0.21	1.27 (0.99-1.61) 0.051	1.40 (0.88-2.23) 0.15	1.22 (0.92-1.60) 0.16	1.43 (1.07-1.91) 0.02	1.18 (0.75-1.84 0.48)	1.39 (1.10-1.76) 0.006
Female to male: no *vs.* yes	0.73 (0.52-1.03) 0.07	0.75 (0.56-1.01) 0.06	1.21 (0.73-2.00) 0.46	0.60 (0.41-1.87) 0.008	1.32 (0.99-1.75) 0.06	1.22 (0.78-1.90) 0.38	1.16 (0.90-1.50) 0.24
DRI: low/int *vs.* high/vhigh	1.57 (1.20-2.06) <0.001	1.60 (1.26-2.02) <0.001	1.12 (0.72-1.73) 0.63	1.84 (1.39-2.44) <0.001	1.09 (0.85-1.40) 0.5	0.97 (0.66-1.44) 0.9	1.39 (1.13-1.72) 0.002
TBI: no *vs.* yes	0.70 (0.52-0.92) 0.01	0.71 (0.55-0.91) 0.007	0.67 (0.42-1.06) 0.09	0.73 (0.55-0.99) 0.04	1.30 (0.99-1.69) 0.06	0.76 (0.51-1.15) 0.19	0.69 (0.55-0.86) <0.001
Age at HSCT: inc. 3 years	1.05 (0.97-1.14) 0.20	0.97 (0.91-1.04) 0.41	1.18 (1.03-1.34) 0.01	0.89 (0.82-0.97) 0.01	0.93 (0.86-1.01) 0.08	1.17 (1.04-1.32) 0.01	1.00 (0.94-1.06 0.97)
Donor age at HSCT: inc. 3 years	0.96 (0.92-1.01) 0.13	0.96 (0.92-1.01) 0.09	1.00 (0.92-1.08) 0.91	0.95 (0.90-0.99) 0.048	1.03 (0.99-1.08) 0.15	1.00 (0.93-1.08) 0.92	0.98 (0.95-1.02) 0.42
Year of HSCT: inc. 5 years	0.79 (0.65-0.95) 0.01	0.89 (0.75-1.05) 0.16	0.88 (0.64-1.21) 0.44	0.88 (0.72-1.07) 0.19	0.99 (0.82-1.20) 0.95	0.98 (0.74-1.31) 0.9	0.86 (0.74-1.01) 0.06
CMV seronegative patients							
Donor CMV: - *vs.* +	1.13 (0.81-1.56) 0.47	1.15 (0.86-1.52) 0.35	1.53 (0.87-2.69) 0.14	1.04 (0.75-1.45) 0.82	1.20 (0.88-1.65) 0.25	0.82 (0.48-1.42) 0.48	1.27 (0.99-1.63) 0.06
Source of cells: BM *vs.* PB	1.05 (0.76-1.44) 0.78	0.99 (0.74-1.31) 0.93	0.71 (0.38-1.31) 0.27	1.09 (0.79-1.50) 0.62	1.43 (1.02-1.99) 0.04	1.53 (0.91-2.58) 0.11	1.04 (0.81-1.34) 0.75
Female to male: no *vs.* yes	0.74 (0.49-1.13) 0.16	0.75 (0.52-1.07) 0.11	0.76 (0.35-1.63) 0.48	0.75 (0.50-1.13) 0.17	1.02 (0.68-1.51) 0.94	1.23 (0.70-2.19) 0.47	0.78 (0.57-1.08) 0.14
DRI: low/int *vs.* high/vhigh	1.11 (0.83-1.50) 0.48	1.39 (1.07-1.81) 0.01	1.04 (0.61-1.78) 0.88	1.53 (1.13-2.06) 0.006	0.88 (0.66-1.18) 0.39	0.71 (0.45-1.14) 0.16	1.32 (1.04-1.66) 0.02
TBI: no *vs.* yes	0.74 (0.55-1.01) 0.05	0.80 (0.62-1.04) 0.09	1.06 (0.61-1.85) 0.82	0.73 (0.54-0.98) 0.04	1.68 (1.24-2.28) <0.001	0.85 (0.52-1.38) 0.5	0.92 (0.73-1.16) 0.46
Age at HSCT: inc. 3 years	1.17 (1.07-1.28) <0.001	1.10 (1.02-1.19) 0.01	1.35 (1.14-1.61) <0.001	1.04 (0.95-1.13) 0.39	0.95 (0.86-1.03) 0.21	1.21 (1.05-1.41) 0.01	1.08 (1.01-1.16) 0.02
Donor age at HSCT: inc. 3 years	1.04 (0.98-1.09) 0.19	1.02 (0.97-1.07) 0.38	1.10 (1.01-1.20) 0.04	1.00 (0.94-1.05) 0.89	1.07 (1.01-1.12) 0.01	1.07 (0.99-1.16) 0.07	1.03 (0.99-1.07) 0.14
Year of HSCT: inc. 5 years	0.94 (0.77-1.15) 0.55	1.01 (0.85-1.20) 0.94	0.91 (0.67-1.40) 0.87	1.01 (0.83-1.24) 0.9	0.88 (0.73-1.06) 0.19	0.92 (0.68-1.25) 0.6	0.81 (0.70-0.94) 0.006

CMV: cytomegalovirus; OS: overall survival; LFS: leukemia-free survival; RI: relapse incidence; NRM: non-relapse mortality; GRFS: graft-*versus*-host disease-free relapse-free survival; aGvHD: acute graft-*versus*-host disease; cGvHD: chronic GCVD; HR: hazard ratio; CI: confidence interval; DRI: disease risk index; TBI: total body irradiation; inc: increments; HSCT: hematopoietic stem cell transplantation; BM: bone marrow; PB: peripheral blood; low/int: low/intermediate; high/vhigh: high/very high.

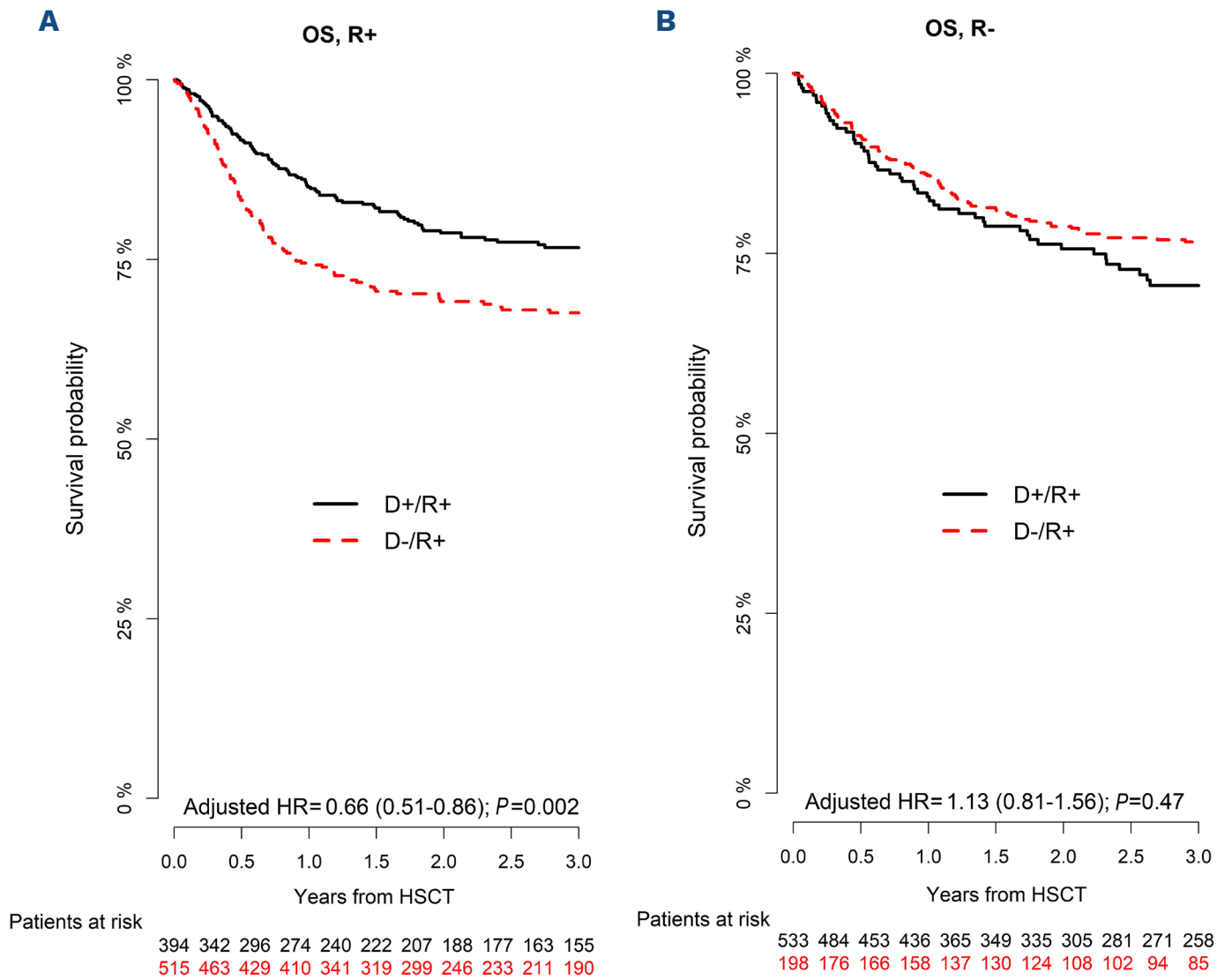

Figure 1. Overall survival in relation to patient and donor cytomegalovirus serology. (A) Kaplan-Meier estimates of overall survial (OS) in seropositive recipient (R+) patients undergoing matched unrelated hematopoietic stem cell transplantation (HSCT) from a seronegative (D- in red) *versus* seropositive (D+ in black) donors. (B) Kaplan-Meier estimates of OS in seronegative recipient (R-) patients undergoing matched unrelated HSCT from a seronegative (D+ in red) *versus* seropositive (D- in black) donors. Shown are adjusted hazard ratios (HR) with 95 % confidence intervals in round brackets.

tients in R- group died (*Online Supplementary Table S3*). Relapse was the main cause of death in all serology categories followed by infections.

Multivariable Cox analysis revealed that several other patient, disease and transplant characteristics besides CMV serology proved significant association with LFS, NRM and RI: for R+ patients LFS was lower for patients with high/vhigh DRI (HR=1.60; *P*<0.001) and higher with TBI use (HR=0.71; *P*=0.007). NRM was higher in older patients (HR=1.18; *P*=0.01). RI was lower for patients with female to male donor (HR=0.60; *P*=0.008), conditioning with TBI (HR=0.73; *P*=0.04), increasing patient (HR=0.89; *P*=0.01) and donor age (HR=0.95; *P*=0.048), but higher for patients with high/vhigh DRI (HR=1.84; *P*<0.001). For R- patients, LFS was lower for patients with high/vhigh DRI (HR=1.39; *P*=0.01) and older patients (HR=1.10; *P*=0.01). Increasing age of the patient and donor was associated with higher NRM (HR=1.35; *P*<0.001 and HR=1.10; *P*=0.04). RI was lower for patients with TBI conditioning (HR=0.73; *P*=0.040) but higher for patients with high/vhigh DRI (HR=1.53, *P*=0.006). The effect of TBI on transplant outcomes were thought to be related to the ALL patients as only 30 AML received TBI. Thus, multivariable Cox analysis validates well known risk factors for LFS, NRM, and RI in this cohort.

In this largest pediatric-only registry study performed to date, a CMV D+ for a CMV R+ was independently associated with significantly better OS (HR=0.66; *P*=0.002), better LFS (HR= 0.75; *P*=0.01) and lower NRM (HR=0.52; *P*=0.004) compared with a CMV D- in 10/10 MUD HSCT. However, no such effect was found in CMV R- patients. To date, some studies including predominantly adults have revealed that CMV serostatus of the donor had no influence on outcome[8] while others reported an advantage of D+ for a R+ patient with better OS and lower TRM[5] and decreased OS in D+/R- transplants.[1] In contrast, our analysis from a large contemporary and purely pediatric cohort comprising more than 1,600 children undergoing allogeneic HSCT for AL shows that even in the current era of DNA-based CMV screening and pre-emptive antiviral therapy selecting a CMV D+ *versus* CMV D- for a CMV-R+ patient is associated with 34% reduced risk for overall death and 48% lower risk for NRM in adjusted analyses.

While our registry-based analysis represents the largest pediatric study to date on the impact of donor CMV serology

on HSCT outcome, it is important to acknowledge inherent limitations. These possibly include occasional discrepancies in the reported CMV serostatus data, the lack of detailed data on CMV reactivation, disease, and treatment, including prophylactic use of letermovir in recent years, as well as other infectious complications. This renders any mechanistic explanation of the effect of CMV donor serostatus on outcome speculative.[11] In addition, cautious interpretation of patient CMV serology results, considering both potential false positives (e.g., adoptive transfer) and negatives (e.g., loss of antibodies during pre-transplant treatment), is mandatory.[12,13] Our findings may significantly influence clinical practice regarding donor selection strategies, particularly when multiple 10/10 HLA-MUD are available. As donor CMV serology had no obvious association with outcome in CMV seronegative children, our study implicates that choosing a D+ might be a wise approach in cases of ambiguous recipient CMV serostatus. Within the well-appreciated limits of cross-study comparisons it is notable that the relative overall mortality risks of CMV mismatching in R+ patients in our study ranges in the same order of magnitude as the negative impact of seven of eight *versus* eight of eight HLA matching and exceeds that of donor age (in 10-year increments) in the recent CIBMTR analysis.[8]

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Contributions

EI, JEG, RM, MI, KK and SC designed the study. JEG and AD collected

and assembled data, performed statistical analysis. EI, JEG and RM wrote the manuscript. ZS, OM-D, FL, PS, JS, J-HD, CR, AB, AL, MB, FF, KK, FR, JB, MT, RFW, CJ, GM, PH and GK provided cases for the study. All authors reviewed and approved the manuscript.

Data-sharing statement

For original data, please contact the corresponding author.

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