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Donor CMV Serostatus Not Predictive of Relapse in D-/R- Pediatric HCT

To the Editor:

Cytomegalovirus (CMV) remains a major cause of complications in hematopoietic cell transplantation (HCT). Recipient CMV serostatus remains a predictor of non-relapse mortality in the ganciclovir era and seronegative recipients with a seronegative donor

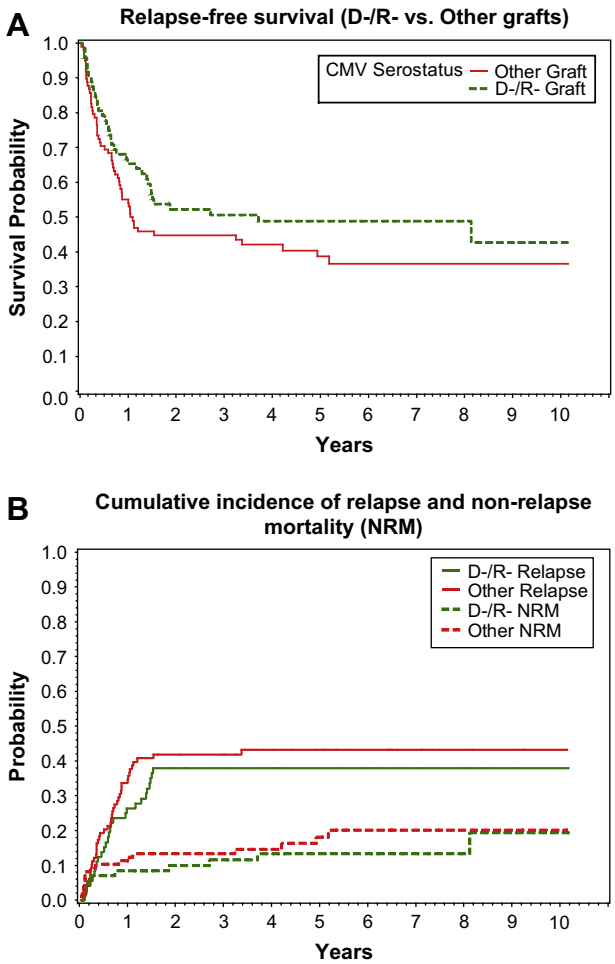

Figure 1. Panel A: relapse-free survival (log-rank p = 0.16). **Panel B**: cumulative incidence of relapse and non-relapse mortality (log-rank p = 0.29 and p = 0.98, respectively).

Table 1. Baseline Characteristics of Pediatric HCT Recipients and Associated Hazards of Relapse and Non-relapse Mortality

Characteristics	Overall n = 170 n (%)	D-/R- Graft n = 72 n (%)	Other Graft n = 98 n (%)	Relapse adj. HR (95% CI)	Non-relapse Mortality (NRM) adj. HR (95% CI)
CMV D-/R-	- -	- -	- -	0.90 (0.54-1.50)	0.67 (0.30-1.4)
Male	103 (61)	47 (65)	56 (57)		
Diagnosis					
ALL	90 (53)	39 (54)	51 (52)	0.68 (0.38-1.23)	0.69 (0.27-1.77)
AML	64 (38)	27 (38)	37 (38)		
MDS	16 (9)	6 (8)	10 (10)		
Disease stage					
Relapse	22 (13)	8 (11)	14 (14.)	4.25 (2.15-8.37) †	1.36 (0.36-5.22)
Others	132 (78)	59 (82)	73 (75)		
Unknown	16 (9)	5 (7)	11 (11)		
Ethnicity					
Caucasian	124 (73)	61 (85)	63 (64.)		
Others	43 (25)	11 (15)	32 (33)		
Unknown	3 (2)	0 (0)	3 (3)		
Donor Type					
Related	73 (43)	25 (35)	48 (49)	1.14 (0.65-2.0)	1.08 (0.46-2.56)
Unrelated	97 (57)	47 (65)	50 (51)		
Donor Age					
0-19 Years	50 (29)	19 (26)	31 (32)		
20-39 Years	67 (39)	30 (42)	37 (38)		
40-55 Years	48 (28)	21 (29)	27 (28)		
55+	5 (3)	2 (2)	3 (3)		
Graft Source					
Bone marrow	119 (70)	51 (71)	68 (69)	0.37 (0.22-0.63) *	0.40 (0.17-0.93) *
PBSC	51 (30)	21 (29)	30 (31)		
Year of transplantation					
1997-2002	110 (65)	47 (65)	63 (64)		
After 2002	60 (35)	25 (35)	35 (36)		
Female-to-male graft					
Yes	56 (33)	22 (31)	34 (35)		
No	114 (67)	50 (69)	64 (65)		
Conditioning regimen					
TBI	136 (80)	60 (83)	76 (78)	1.34 (0.58-3.09)	1.37 (0.37-5.08)
Other	30 (18)	11 (15)	19 (19)		
Missing	4 (2)	1 (1)	3 (3)		
Acute GVHD					
Grade 2-4	150 (88)	66 (92)	84 (86)	0.92 (0.42-2.01)	0.65 (0.20-2.14)
Grade 0-1	20 (12)	6 (8)	14 (14)		

*p value < 0.05

†p value < 0.001, all factors in multivariate Cox proportional hazards model have associated hazard ratios as shown in the table.

(D-/R-) have shown an improved outcome in several recent studies [1,2]. It is currently recommended that seronegative recipients receive a graft from a seronegative donor whenever possible [3]. We therefore read with interest the article by Behrendt et al. that demonstrates that children undergoing primary myeloablative HCT have an increased risk of relapse in D-/R- grafts, and that there was no impact of recipient or donor CMV serostatus on non-relapse mortality [4].

We replicated the analyses with identical inclusion criteria and methods. In our sample we analyzed 170 children from 0-18 years of age who underwent primary, myeloablative, non T-cell depleted allogeneic HCT at the Fred Hutchinson Cancer Research Center and Seattle Children's Hospital from 1997 through 2005. All patients underwent CMV surveillance and received preemptive antiviral therapy with ganciclovir (or foscarnet if neutropenic); all patients received low-dose acyclovir for herpes simplex and varicella zoster virus prophylaxis [5]. Our sample was different in ethnic makeup and prior conditioning regimens (Table 1), but otherwise our populations were comparable. In contrast to their study, in univariate analysis we did not find a difference in median relapse-free survival (log-rank test, p = 0.16) when comparing D-/R- subjects and other grafts (Figure 1A). Similarly, in a multivariate Cox proportional hazards model with similar adjustments, D-/R- transplant recipients were not at higher risk for relapse (HR 0.9, 95% CI 0.54-1.50). There was also no difference in relapse or non-relapse mortality when comparing D-/R- and other grafts (Figure 1B).

Our study results are in contrast to the study by Behrendt et al. Since these data are generated at two separate centers, many factors could have led to conflicting results. These differences could potentially be explained by the different racial/ethnic make-up of their cohort (a higher incidence of Hispanics), and we would be interested if these findings are similar after adjustment for these characteristics. Differences in the conditioning regimens (e.g. in the use of etoposide) could also be important. Given that they

describe an age distribution peak at age 1 [4], a third possible explanation could be a larger proportion in their cohort with infant leukemia. Since these subjects would be more likely to have poor outcomes and be CMV seronegative [6], this may have altered the risk associated with D-/R- grafts. Most importantly, the small number of subjects is a limitation of both of these analyses.

In summary, we were not able to replicate the findings in the study by Behrendt et al. Because of the unexpected findings in their study, the larger implications on donor matching, and the relative lack of data in children, an assessment of larger longitudinal datasets such as the CIBMTR or EBMT is warranted. We believe that current recommendations to use CMV seronegative grafts for pediatric seronegative recipients should not be abandoned until further studies can confirm or refute these findings.

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