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Impact of Donor and Patient CMV Serology in Children Receiving First Geno-Identical or Unrelated HSCT for Malignant Hematological Disease: An EBMT Retrospective Registry Study

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In a large registry-based study in children the impact of donor (D) and recipient (R) CMV serology on transplant outcomes in malignant hematological diseases was evaluated. Pediatric patients (age <18) reported to European Society for Blood and Marrow Transplantation (EBMT) who received an unmanipulated transplant from a matched sibling (MSD) or an unrelated donor (UD) (10/10, 9/10 HLA match) with bone marrow (BM) or peripheral blood stem cells (PB) between 2007 and 2020 were included. Patients receiving haploidentical grafts, cord blood and *ex vivo* T-cell depletion were excluded. Impact of D and R CMV serology on overall survival (OS), progression free survival (PFS), relapse incidence (RI) and non-relapse mortality (NRM) was evaluated in 4 categories (D-/R-, D-/R+, D+/R-, D+/R+), within MSD, UD10/10 and UD9/10 groups. Variables used for adjustment were source of cells, age at transplant, female to male transplant, year of transplant, disease risk index, and total body irradiation use.

There were 7033 transplants with a median follow-up of 3.5 yrs. In total 3407, 2599 and 1027 patients received MSD, UD10/10 and UD9/10 transplants, respectively (Table I). In multivariable Cox models (Table II), MSD with the combinations D+/R+ and D-/R+ had significantly decreased OS (HR, 1.22; p=0.03 and HR, 1.26; p=0.04, respectively) and increased NRM (HR, 1.63; p=0.008 and HR, 2.01; p=<0.001, respectively) compared to D-/R-. The PFS was significantly decreased in D-/R+ (HR, 1.22; p=0.04) compared to D-/R- and not significantly different for D+/R+. For D+/R-, RI was significantly lower (HR 0.71; p= 0.03) without significant increase of NRM (HR 1.5. p=0.15) and non-significantly different PFS (HR 0.83, p=0.17) but RI was not significantly different for D+/R+ and D-/R+ compared to D-/R- (HR 1.06; p=0.47 and HR 1.08; p=0.5, respectively). UD10/10, D-/R+ had a significantly decreased OS (HR, 1.55; p=<0.001), decreased PFS (HR, 1.37; p=<0.001), increased NRM (HR, 2.03; p=<0.001) compared to D-/R- group. There were no significant differences in other groups. In UD9/10, there was no significant difference in OS between groups. Significantly increased NRM (HR, 1.6; p=0.03) was observed in D-/R+ group. Collectively, our data in a large, registry-based analysis show that CMV serology remains to have a substantial impact on survival in both MSD and UD10/10 transplants in children transplanted for malignant hematological diseases. For MSD, the D-/R+ and D+/R+ combinations have decreased OS and increased NRM compared to D-/R- and donor serology is not of significant impact on OS and PFS in both R+ and R- patients. RI was significantly lower in D+/R- in MSD which may be due to the possible "virus versus leukemia" effect as suggested by previous studies. However, this did not translate into improved PFS. For UD10/10, only D-/R+ (but not D+/R+ or D+/R-) have decreased OS and increased NRM compared to D-/R- transplants. This observation is clearly different from previous registry based studies focusing on adults where D+/R- transplants were also reported to have decreased OS compared to D-/R-. Our study reveals that for UD10/10 transplants selection of serocompatible donor is pivotal in R+ patients for transplants in children with malignant hematological diseases. In conclusion, this large retrospective trial shows that CMV serology represents a substantial determinant of survival in both MSD and UD10/10 transplants in children transplanted for a malignant hematological disease. While selecting donor according to CMV serology has no impact on survival for MSD transplants, selection of a serocompatible donor for a seropositive patient significantly improves overall survival in the unrelated donor setting, which represents a clinically impactful finding.

Table I: Transplant characteristics and outcomes in MSD and UD transplants

Variables		MSD	UD 10/10	UD 9/10
Patient number (%)	n= 7033	N=3407 (48%)	N=2599 (36%)	N=1027 (14%)
Age at transplant		10.2 (0.2-18)	9.0 (0.3-18)	9.3 (0.4-18)
Patient sex	Male	2128 (62.5)	1585 (61)	620 (60.4)
	Female	1279 (37.5)	1014 (39)	407 (39.6)
CMV Serology	D-/R-	N=840 (24%)	814 (31%)	277 (26%)
	D-/R+	N=503 (14%)	680 (26%)	292 (28%)
	D+/R-	N=250 (7%)	295 (11%)	129 (12.5%)
	D+/R+	N=1814 (53%)	810 (31%)	329 (32%)
Disease	ALL	1770 (52)	1310 (50.4)	523 (50.9)
	AML	1132 (33.2)	747 (28.7)	291 (28.3)
	MDS	172 (5)	239 (9.2)	82 (8)
	MDS & MPN	87 (2.6)	112 (4.3)	51 (5)
	MPN	9 (0.3)	7 (0.3)	4 (0.4)
	Hodgkins	46 (1.4)	27 (1)	11 (1.1)
	NHL	96 (2.8)	94 (3.6)	39 (3.8)
	CML	95 (2.8)	63 (2.4)	26 (2.5)
DRI	Low	226 (6.6)	150 (5.8)	65 (6.3)
	Int	1852 (54.4)	1334 (51.3)	512 (49.9)
	High	1204 (35.3)	1031 (39.7)	411 (40)
	Very high	125 (3.7)	84 (3.2)	39 (3.8)
Year of transplant	median (range)	2013 (2007-2020)	2014(2007-2020)	2014 (2207-2020)
Female to male	No	2419 (71)	2159 (83.1)	806 (78.5)
	Yes	988 (29)	440 (16.9)	221 (21.5)
Source of cells	BM	2438 (71.6)	1655 (63.7)	663 (64.6)
	PB	969 (28.4)	944 (36.3)	364 (35.4)
Myeloablative regimen	No	114 (3.4)	124 (4.8)	43 (4.2)
	Yes	3285 (96.6)	2451 (95.2)	969 (95.8)
	missing	8	24	15
TBI	No	1991 (58.4)	1629 (62.7)	617 (60.1)
	Yes	1416 (41.6)	970 (37.3)	410 (39.9)
GVHD prophylaxis	CSA	1167 (34.3)	412 (15.9)	114 (11.1)
	CSA+MTX	1971 (57.9)	1745 (67.1)	705 (68.6)
	CSA+MTX+Other	27 (0.8)	57 (2.2)	18 (1.8)
	CSA+Other	117 (3.4)	129 (5)	68 (6.6)
	Other not including CSA	125 (3.7)	256 (9.8)	122 (11.9)
Outcomes (estimation (95%CI))	OS	69.3 (67.5 - 71)	68.9 (66.9 - 70.7)	65.4 (62.2 - 68.4)
	PFS	59.9 (58.1 - 61.8)	60.8 (58.7 - 62.7)	59.3 (56 - 62.4)
	RI	31.6 (29.8 - 33.3)	27.2 (25.4 - 29)	22.9 (20.2 - 25.6)
	NRM	8.5 (7.5 - 9.5)	12 (10.8 - 13.4)	17.9 (15.5 - 20.4)

Table II. Transplant outcomes in different type of transplants in each D/R pair compared to D-/R-

	Outcome	OS	PFS	NRM	RI
MSD	D-/R+	Decreased (p=0.04)	Decreased (p=0.04)	Increased (p=<0.001)	NS (p=0.5)
	D+/R-	NS (p=0.32)	NS (p=0.17)	NS (p=0.16)	Decreased (p=0.03)
	D+/R+	Decreased (p=0.03)	NS (p=0.08)	Increased (p=0.008)	NS (p=0.47)
UD10/10	D-/R+	Decreased (p<0.001)	Decreased (p<0.001)	Increased (p<0.001)	NS (p=0.26)
	D+/R-	NS (p<0.34)	NS (p=0.52)	NS (p=0.18)	NS (p=0.93)
	D+/R+	NS (p=0.17)	NS (p=0.36)	NS (p=0.16)	NS (p=0.91)
UD9/10	D-/R+	NS (p=0.54)	NS (p=0.52)	Increased (p=0.03)	NS (p=0.18)
	D+/R-	NS (p=0.68)	NS (p=0.85)	NS (p=0.73)	NS (p=0.56)
	D+/R+	NS (p=0.58)	NS (p=0.28)	NS (p=0.26)	NS (p=0.66)

NS: Not significant

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164538
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Preferred Presentation Format:
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