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The Impact of Donor CMV Serostatus on Outcomes of CMV Infections After Hematopoietic Cell Transplantation

#2121

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Background

- Cytomegalovirus (CMV) infection remains a significant complication after allogeneic hematopoietic cell transplant (allo-HCT) and may have a deleterious impact on overall outcomes.
- CMV infection may be associated with increased risk of graft versus host disease (GVHD), myelosuppression, and bacterial, fungal and viral infections.
- Primary prophylaxis (PP) with letermovir significantly reduces the risk of clinically significant CMV infection (CS-CMVi).
- The impact of recipient CMV serostatus on CS-CMVi and long term HCT outcomes has been well described but the impact of donor CMV serostatus remains unclear.

Study Objective

- To analyze the significance of donor CMV serostatus in a large cohort of allo-HCT recipients

Methods

- This is a single-center, retrospective cohort study of 651 allo-HCT recipients cared for at our institution between March 2016 and December 2018.
- Data on baseline demographics, transplant characteristics, preventive strategies, CMV infection, and transplant-related outcomes (development of GVHD, all-cause and non-relapse mortality) were collected.
- Donor CMV serology (seropositive (D+) or seronegative donor (D-)) and recipient CMV serology (seropositive (R+) or seronegative recipients (R-)) were used to identify four groups of interest for analysis purposes.
- A univariate analysis was performed for outcomes of interest using CMV serostatus D-/R- as a control group.
- CS-CMVi was defined as CMV disease or CMV viremia leading to preemptive treatment.

Results

- Out of the 651 allo-HCT recipients, 77 were D-/R-, 43 D+/R-, 290 D+/R+, and 241 D-/R+ (Table 1).
- Most patients underwent HCT for AML (40%), received myeloablative conditioning (51%), and had a matched unrelated donor (MUD) HCT (46%).
- In 2018, letermovir was used for PP in 27% of the D+/R+, 18% of the D-/R+ allo-HCT recipients (Table 1) for a total of 116 (55%) allo-HCT recipients.

Table 1

Table 1. Baseline characteristics

Characteristic	D-/R- (n=77)	D+/R+ (n=290)	D-/R+ (n=241)	D+/R- (n=43)	p-value
Age, median (range)	57 (17-74)	55 (5-73)	54 (18-77)	58 (15-70)	0.7503
Gender*					
Female	26 (33.8)	131 (45.2)	122 (50.6)	15 (34.9)	0.0325
Male	51 (66.2)	159 (54.8)	119 (49.4)	28 (65.1)	
Race					
Asian	0 (0%)	16 (5.5%)	7 (2.9%)	1 (2.3%)	0.0969
African American	7 (9.1%)	25 (8.6%)	12 (5%)	4 (9.3%)	0.3546
Hispanic/Latino*	11 (14.3%)	61 (21.0%)	25 (10.4%)	3 (7.0%)	0.0027
Middle Eastern*	1 (1.3%)	24 (8.3%)	4 (1.6%)	0 (0%)	0.0004
White*	58 (75.3%)	160 (55.2%)	188 (78.0%)	34 (79.1%)	<0.0001
Other	0 (0%)	4 (1.4%)	5 (2.1%)	1 (2.3%)	0.5960
Indication for transplant					
ALL*	3 (3.9%)	40 (13.8%)	33 (13.7%)	1 (2.3%)	0.0166
AML*	16 (20.8%)	139 (48.0%)	98 (40.7%)	6 (14%)	<0.0001
Acute bi-phenotypic leukemia	0 (0%)	1 (0.3%)	5 (2.1%)	0 (0%)	0.1282
Aplastic anemia	0 (0%)	4 (1.4%)	5 (2.1%)	1 (2.3%)	0.5960
CLL/SLL	8 (10.4%)	10 (3.4%)	9 (3.7%)	2 (4.6%)	0.0613
CML	7 (9%)	7 (2.4%)	14 (5.8%)	3 (7.0%)	0.0513
CMML	2 (2.6%)	11 (3.8%)	3 (1.3%)	1 (2.3%)	0.3372
MDS	10 (13%)	38 (13.1%)	32 (13.3%)	11 (25.6%)	0.1604
MF	11 (14.3%)	20 (6.9%)	23 (9.5%)	7 (16.3%)	0.0819
NHL*	10 (13%)	12 (4.1%)	10 (4.1%)	6 (14%)	0.0017
Other*	10 (13%)	8 (2.8%)	9 (3.7%)	5 (11.6%)	0.0003
HCT Type					
MRD*	21 (27.3)	105 (36.2)	55 (22.8)	12 (28.0)	0.0087
MUD*	40 (51.9)	98 (33.8)	143 (59.3)	20 (46.5)	<0.0001
MMUD	0 (0)	4 (1.4)	3 (1.3)	1 (2.3)	0.6965
Haploidentical*	15 (19.5)	63 (21.7)	34 (14.1)	9 (20.9)	0.1526
Cord*	1 (1.3)	20 (6.9)	6 (2.5)	1 (2.3)	0.0326
Myeloablative conditioning*	17 (22.1)	149 (51.3)	134 (55.6)	30 (69.8)	<0.0001
HCT Source					
Marrow*	16 (20.8)	78 (26.9)	89 (36.9)	11 (25.6)	0.0156
Peripheral*	60 (77.9)	192 (66.2)	146 (60.6)	31 (72.1)	0.0331
Cord*	1 (1.3)	20 (6.9)	6 (2.5)	1 (2.3)	0.0326
Time to engraftment in days, median (range)*	16 (9-376)	15 (2-384)	13 (5-36)	17 (2-30)	0.0210
ATG*	13 (16.9%)	66 (22.7%)	88 (36.5%)	9 (20.9%)	0.0003
Post-Cy	45 (58.4%)	141 (48.6%)	94 (39.0%)	26 (60.5%)	0.0034
CMV prophylaxis					
Lead in GCV*	14 (18.2%)	84 (29.0%)	39 (16.2%)	11 (25.6%)	0.0064
Letermovir primary prophylaxis*	0 (0%)	79 (27.2%)	44 (18.2%)	0 (0%)	<0.0001

** P value <0.05*
Abbreviations: D: donor, R: Recipient, ALL: acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CLL/SLL: Chronic lymphoblastic leukemia/small lymphocytic leukemia; CML: chronic myeloid leukemia; CMML: Chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; MF: myelofibrosis; NHL: non-Hodgkin lymphoma ; HCT: hematopoietic cell transplantation; MRD: Match related donor; MUD: match unrelated donor: MMUD: mismatched unrelated donor; ATG: antithyroglobulin; Post-Cy: post cyclophosphamide; CMV: cytomegalovirus; GCV: ganciclovir

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- Compared to the CMV D-/R- group, D+/R+ and D-/R+ groups (Table 2) had a greater incidence of CS-CMVi (3.9% vs. 40% vs. 50.6%; all p<0.01, respectively), CMV end organ disease (0% vs. 14.8% vs. 19.1%; all p<0.001, respectively), and refractory/resistant (R/R) CMV infections (0% vs. 5.5% vs. 12.4%; all p<0.03, respectively) within 48 weeks of allo-HCT.
- CS-CMVi and R/R CMV was more common in D-/R+ allo-HCT when compared to D+/R+ group (50.6% vs. 40.0%, p<0.001).
- Non-relapse mortality at day 100 in all R+ Allo-HCT recipients was numerically greater than D-/R- (3.9% vs 10.0%; 0.0931).
- D-/R+ allo-HCT had higher non-relapse mortality at day 100 compared to D-/R- (3.9% vs. 10.8%, p=0.07).

Table 2

Table 2. Outcome analysis

Variable	D-/R- (n=77)	D+/R- (n=43)	p- value[1]	D+/R+ (n=290)	p-value[1]	D-/R+ (n=241)	p-value[1]	p-value [2]
CMV within 48 weeks								
CS-CMVi*	3 (3.9)	4 (9.3)	0.2480	116 (40.0)	<0.0001*	122 (50.6)	<0.0001*	0.0179*
CMV end-organ disease	0 (0)	1 (2.3)	0.3583	43 (14.8)	<0.0001*	46 (19.1)	<0.0001*	0.2433
R/R CMV	0 (0)	1 (2.3)	0.3583	16 (5.5)	0.0291*	30 (12.4)	0.0002*	0.0052*
GVHD								
GVHD at day 100	31 (40.3)	21 (48.8)	0.5338	134 (46.2)	0.1032	123 (51.0)	0.3639	0.2955
GVHD at week 48	49 (63.6)	27 (62.8)	1.0000	143 (49.3)	0.0291*	133 (55.2)	0.2338	0.1911
Outcomes								
All-cause mortality at day 100	5 (6.5)	3 (7.0)	1.0000	33 (11.4)	0.2923	28 (11.6)	0.2825	1.0000
All-cause mortality at week 24	16 (20.8)	5 (11.6)	0.3161	52 (17.9)	0.6207	49 (20.3)	1.000	0.5065
All-cause mortality at week 48	18 (23.4)	7 (16.3)	0.4829	86 (29.6)	0.3205	79 (32.8)	0.1547	0.4524
Non-relapse mortality at day 100	3 (3.9)	2 (4.6)	1.0000	27 (9.3)	0.1609	26 (10.8)	0.0720	0.6630
Non-relapse mortality at week 24	8 (10.4)	1 (2.3)	0.2680	36 (12.4)	0.8430	39 (16.2)	0.2695	0.2600
Non-relapse mortality at week 48	11 (14.3)	2 (4.6)	0.2153	54 (18.6)	0.5005	53 (22.0)	0.1902	0.3848

** P value <0.05*
[1]Univariate analysis using D-/R- as a control
[2] Univariate analysis comparing D+/R+ to D-/R-
Abbreviations: D: donor, R: Recipient; CMV: cytomegalovirus; CS-CMVi: Clinically significant CMV infection; R/R CMV: CMV; GVHD: Graft versus host disease.

Conclusions

• Allo-HCT recipients with CMV seronegative donor and recipient had less CMV related complications and a trend towards better survival when compared to D-/R+ allo-HCT.

• CMV D-/R+ HCT recipients had greater CMV related complications when compared to CMV D+/R+ HCT recipients, possibly due to the protective effect of donor seropositivity.

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