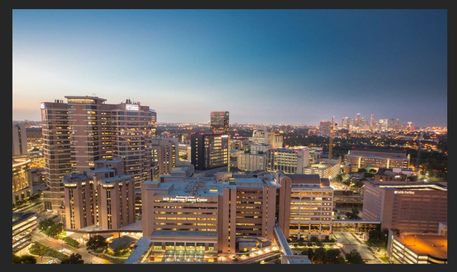

The Impact of HHV–6 DNAemia on Hematopoietic Cell Transplant (HCT) Recipients at High Risk for CMV Reactivation in the era of Letermovir

#2122

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BACKGROUND

- Letermovir (LTV) has reduced non–relapse mortality (NRM) in allogeneic hematopoietic cell transplant (allo–HCT) recipients by reducing the rate of clinically significant cytomegalovirus infections (CS-CMVi) in sero-positive recipients (R+); the impact of LTV prophylaxis (PP) on other infections is unclear.
- Human herpesvirus 6 (HHV–6) is a common infectious cause of encephalitis after HCT but its natural history and its interaction with CMV is incompletely understood after allogeneic HCT.

OBJECTIVE

- To investigate the effects of Letermovir prophylaxis on human HHV–6 DNAemia in HCT recipients with or without CS-CMVi

METHODS

- Single-center, retrospective cohort study (March 2016 – December 2018)
- Consecutive R+ allo-HCT recipients with or without LTV PP were included
- Baseline demographics, transplantation characteristics, CMV and HHV-6 data were collected
- Outcomes of interest included NRM at 100 days, 24 and 48 weeks post alloHCT
- Univariate analysis to determine factors associated with HHV-6 DNAemia, CS-CMVi, and NRM was performed using Fischer exact test or Wilcoxon rank sum as appropriate. Logistic regression to identify independent variables associated with HHV-6 DNAemia and NRM was performed.

RESULTS

Table 1. Baseline patient characteristics of allo-HCT recipients stratified by HHV-6 DNAemia.

Characteristic	HHV-6 DNAemia (n = 111)	No HHV-6 DNAemia (n = 428)	Total (n = 539)	p-value
Age, median (range)	48 (11-77)	56 (5-73)	54 (5-77)	0.0004*
Age >40 years (%)	68 (61)	329 (77)	397 (74)	0.0015*
Gender				
Female (%)	49 (44)	209 (49)	258 (48)	0.3953
Male (%)	62 (56)	219 (51)	281 (52)	
Race				
Asian (%)	5 (5)	18 (4)	23 (4)	0.7975
African American (%)	14 (13)	25 (6)	39(7)	0.0220*
Hispanic/Latino (%)	23 (21)	63 (15)	86 (16)	0.1452
Middle Eastern (%)	6 (5)	22 (5)	29 (5)	0.6378
White (%)	60 (55)	293 (68)	353 (65)	0.0051*
Other (%)	2 (2)	7 (2)	9 (2)	1.0000
Indication for Transplant				
ALL (%)	27 (24)	48 (11)	75 (14)	0.0010*
AML (%)	43 (39)	197 (46)	240 (45)	0.1984
Acute bi-phenotypic leukemia (%)	1 (1)	5 (1)	6 (1)	1.0000
Aplastic anemia (%)	4 (4)	5 (1)	9 (2)	0.0919
CLL/SLL (%)	1 (1)	18 (4)	19 (4)	0.1442
CML (%)	4 (4)	17 (4)	21 (4)	1.0000
CMML (%)	4 (4)	10 (2)	14 (3)	0.5011
MDS (%)	17 (15)	55 (13)	72 (13)	0.5312
MF (%)	4 (4)	39 (9)	43 (8)	0.0746
NHL (%)	3 (3)	19 (4)	22 (4)	0.5915
Other (%)	3 (3)	15 (3)	18 (3)	1.0000
Myeloablative conditioning (%)	37 (33)	249 (58)	286 (53)	<0.0001*
HCT Type				
MRD (%)	13 (12)	153 (36)	166 (31)	<0.0001
MUD (%)	25 (23)	223 (52)	248 (46)	<0.0001*
MMUD (%)	0 (0)	7 (2)	7 (1)	0.3542
Haploidentical	56 (50)	43 (10)	99 (18)	<0.0001*
Cord blood (%)	17 (15)	9 (2)	26 (5)	<0.0001*
HCT Source				
Marrow (%)	52 (47)	116 (27)	168 (31)	0.0001*
Peripheral (%)	42 (38)	303 (71)	345 (64)	<0.0001*
Cord (%)	17 (15)	9 (2)	26 (5)	<0.0001*
ATG (%)	27 (25)	127 (30)	154 (29)	0.2903
Post-Cy (%)	61 (55)	176 (41)	237 (44)	0.0100*
GVHD ≤48 weeks post-HCT (%)	63 (57)	217 (51)	280 (52)	0.2867
CS-CMVi (%)‡	66 (59)	175 (41)	241 (45)	0.0006*
CMV prophylaxis				
Lead in GCV (%)	69 (63)	51 (12)	121(22)	<0.0001*
Letermovir (%)	19 (17)	105 (25)	124 (23)	0.1018

** p<0.05*
‡ Adjusted p-value; OR (95% CI)† = 0.0472; 1.69 (1.00-2.82)
†For the purpose of Logistic regression model, all cell sources were analyzed as Marrow/Cord vs Periphery
***Abbreviations**: HHV6, human herpesvirus 6; CS-CMVi, clinically significant cytomegalovirus infection; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL/SLL, chronic lymphocytic leukemia and small lymphocytic lymphoma; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin Lymphoma; MF, myelofibrosis; allo-HCT, allogeneic hematopoietic cell transplant; MRD, matched related donor; MUD, matched unrelated donor; GVHD, graft-versus-host-disease; ATG, anti-thymocyte globulin; Cy, cyclophosphamide.*

Table 2. Univariate and Multivariate analysis for risk factors for non-relapse mortality at week 48.

Characteristics	48-week survival N=347	48-week mortality N=100	p value	Adjusted p value; OR (95% CI)
Age, median (range)	53 (5-73)	57 (21-77)	0.0777	
Age >40 years (%)	246 (71)	82 (82)	0.0290*	0.0051; 2.21 (1.24-3.95)
Gender				
Male (%)	189 (54)	42 (42)	0.0311*	0.0625
Female (%)	158 (46)	58 (58)		
Race				
White (%)	224 (65)	72 (72)	0.1874	
Middle eastern (%)	19 (5)	4 (4)	0.7972	
Hispanic (%)	61 (18)	14 (14)	0.4502	
Black (%)	25 (7)	6 (6)	0.8246	
Asian (%)	13 (4)	3 (3)	1.0000	
Other (%)	5 (1)	1 (1)	1.0000	
Indication for transplant				
Acute leukemia (%)	5 (1)	1 (1)	1.0000	
ALL (%)	51 (15)	13 (13)	0.7476	
AML (%)	145 (42)	40 (40)	0.8180	
AA (%)	7 (2)	2 (2)	1.0000	
CLL/SLL (%)	14 (4)	1 (1)	0.2081	
CML (%)	17 (5)	3 (3)	0.5856	
CMML (%)	11 (3)	3 (3)	1.0000	
MDS (%)	44 (13)	17 (17)	0.3205	
MF (%)	32 (9)	9 (8)	1.0000	
NHL (%)	13 (4)	5 (5)	0.5675	
Other (%)	8 (2)	6 (6)	0.0951	
Myeloablative conditioning (%)	189 (54)	45 (45)	0.1116	
HCT Type				
MUD (%)	156 (45)	49 (49)	0.4958	
MRD (%)	110 (32)	14 (14)	0.0004*	0.0016; 0.36 (0.18-0.70)
MMUD (%)	5 (1)	2 (2)	0.6560	
Haplo (%)	67 (17)	32 (32)	0.0018*	0.4641
Cord (%)	17 (5)	3 (3)	0.4476	
HCT source				
Marrow (%)	103 (30)	42 (42)	0.0287*	0.6463
Cord (%)	17 (5)	3 (3)	0.5856	
Periphery (%)	227 (65)	55 (55)	0.0608	
Post Cy (%)	160 (46)	46 (46)	1.0000	
ATG (%)	92 (27)	36 (36)	0.0785	
GVHD within 48 weeks (%)	177 (51)	57 (57)	0.3081	
CMV prophylaxis				
Lead in GCV (%)	72 (21)	34 (34)	0.0076*	0.9920
Letermovir prophylaxis (%)	80 (23)	16 (16)	0.1664	0.1843
Viral infections				
CS-CMVi (%)	145 (42)	63 (63)	0.0002*	0.0382*; 1.67 (1.03-2.62)
HHV6 DNAemia (%)	67 (19)	32 (32)	0.0093*	0.2222

**p<0.05*
***Abbreviations**: HHV6, human herpesvirus 6; CS-CMVi, clinically significant cytomegalovirus infection; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL/SLL, chronic lymphocytic leukemia and small lymphocytic lymphoma; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin Lymphoma; MF, myelofibrosis; HCT, hematopoietic cell transplant; MRD, matched related donor; MUD, matched unrelated donor; GVHD, graft-versus-host-disease; ATG, anti-thymocyte globulin; Cy, cyclophosphamide.*

Results

- A total of 539 allo–HCT recipients were included in our analysis; 124 (23%) received and 415 (77%) did not LTV PP.
- HHV–6 DNAemia was identified in 111 (21%) alloHCT recipients within the first year of transplant, where CS-CMVi occurred in 241 (45%) (table 1).
- Risk factors for HHV–6 DNAemia included African American race, underlying ALL, Haploidentical or cord HCT, marrow or cord source of stem cells, use of cyclophosphamide, and CS-CMVi (Table 1).
- On multivariate analysis, CS-CMVi was the only independent predictor of HHV–6 DNAemia (Adjusted OR: 1.69).
- Independent predictors of NRM on logistic regression included CS-CMVi (OR: 1.67, CI 95% 1.03–2.62), age > 40 years (OR: 2.21, CI 95% 1.24–3.95), and matched related donor allo–HCT (OR: 0.36, CI 95% 0.18–0.70) as a protective factor (Table 2).

CONCLUSION

- Our preliminary analysis identified CS-CMVi as a risk factor for HHV-6 DNAemia, but did not demonstrate a clear correlation with letermovir use.
- CS-CMVi is associated with NRM in line with prior studies.
- Larger studies are needed to better elucidate the interaction between HHV-6 and CS-CMVi and the impact of LTV PP.

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