Comparison of Cytomegalovirus DNA Load in Whole Blood and Plasma of Transplant Recipients with CMV Infection and Disease

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Background

Cytomegalovirus (CMV) causes significant morbidity after solid organ (SOT) and hematopoietic stem cell transplantation (HSCT). Currently, quantitative nucleic acid test (QNAT) is the most common method for diagnosis and monitoring treatment of CMV disease.

CMV viral load (VL) can be quantified in plasma (PL) and whole blood (WB). Prior studies suggested that WB is a more sensitive sample, with earlier detection of viremia, and at higher VL levels, when compared to PL. Whether this increased sensitivity is clinically beneficial remains debatable.

The First WHO International Standard for CMV QNAT was released in 2010. To date, there have only been a limited numbers of studies that correlated PL and WB measurements of CMV VL, using a test calibrated to the WHO International Standard.

We prospectively quantified CMV DNA in paired PL and WB from SOT and HSCT recipients diagnosed and treated for CMV disease. We aimed primarily to compare the results between these 2 compartments tested with a CMV QNAT calibrated to the WHO International Standard. In the process, we also defined viral load thresholds that distinguish CMV asymptomatic from symptomatic disease which could assist in determining the CMV VL threshold values for preemptive therapy.

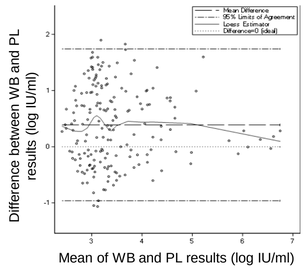
Demographic data

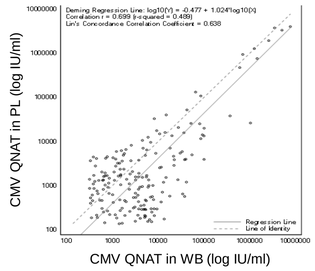
Patient characteristic	No. patients with data available	Result
Age (in years) at time of transplant	88	56.7 (47.8, 63.0)^
Male gender	88	54 (61%)
Caucasian	87	75 (86%)
Year of transplant	88	2013 [1989, 2015]*
Type of transplant:	88	
Solid organ		46 (52%)
HSCT, autologous		3 (3%)
HSCT, allogenic		39 (44%)
CMV status, pre-transplant, SOT & HSCT groups	78	
D+R-		17 (22%)
D+R+		36 (46%)
D-R+		25 (32%)
CMV status, pre-transplant, SOT subgroup	43	
D+R-		17 (40%)
D+R+		18 (42%)
D-R+		8 (19%)
CMV status, pre-transplant, HSCT subgroup	35	
D+R-		0 (0%)
D+R+		18 (51%)
D-R+		17 (49%)
Year of CMV infection	88	2014 [2013, 2015]*
Type of CMV infection	88	
Asymptomatic		57 (65%)
Syndrome (all SOT recipients)		11 (13%)
Tissue-invasive		20 (23%)
Initial VL (IU/mL), plasma	83	954 (363, 4,880)^
Initial VL (IU/mL), whole blood	83	5,480 (1740, 18,200)^
Peak VL (IU/mL), plasma	88	1,380 (442, 5,690)^
Peak VL (IU/mL), whole blood	88	6,240 (2,020, 22,400)^
Patients free of relapse (since end of treatment)	88	
6 months		82% (12)+
1 year		74% (16)+
2 years		74% (16)+
Event total		16
Patients free of death (since end of treatment)	88	
6 months		76% (21)+
1 year		73% (24)+
2 years		58% (31)+
Event total		31
Patients free of death (since transplant)	88	
6 months		90% (9)+
1 year		82% (16)+
2 years		67% (26)+
10 years		59% (27)+
Event total		31

^ Median (25th, 75th percentiles)
* Median [minimum, maximum]
+ Kaplan-Meier estimate (no. of events)
Note: Peak VL for PL and WB were derived from the highest CMV VL values observed in each subject during the course of the study.

Agreement of CMV VL in WB and PL (All Subjects)

CMV VL in PL	CMV VL in WB			Overall agreement (%)	Kappa (95% CI)
	Target not detected	Detected, but <LLoQ	Quantifiable		
Target not detected	72 (17.9%)	9 (2.2%)	0 (0.0%)	279 / 403 (69.2%)	0.49 (0.43, 0.56)
Detected, but <LLoQ	44 (10.9%)	22 (5.5%)	5 (1.2%)		
Quantifiable	17 (4.2%)	49 (12.2%)	185 (45.9%)		

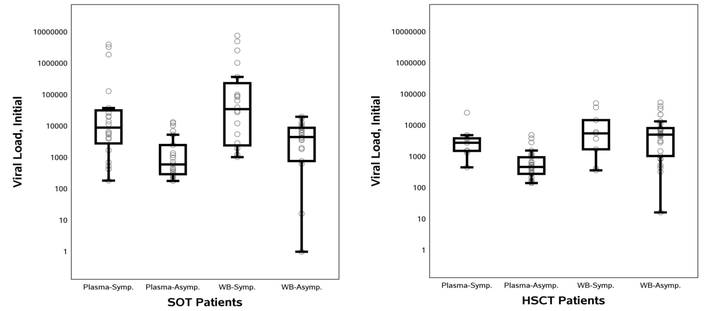




Conclusions

- There was modest agreement in CMV VL between PL and WB, with 31% of pair samples showing discordant results, mostly due to PL measurements being more sensitive in detecting low CMV VL.
- Median initial CMV VL was generally higher in those with symptomatic disease than those with asymptomatic viremia, which was consistently found in PL measurements for both SOT and HSCT, but not WB in HSCT group.
- ROC analyses suggest a CMV VL threshold of 1,350 IU/mL in PL for our HSCT and 1,700 IU/mL for our SOT groups to distinguish asymptomatic from symptomatic disease and as a guide to initiate antiviral therapy in those on pre-emptive monitoring (furthers studies needed to support clinical use).

Boxplots, Initial VL in PL and WB in SOT and HSCT Recipients



SOT Recipients	N	Symptomatic	Asymptomatic	P value
Initial VL, Plasma^	43	9100 (2,830, 32,200)	606 (297, 2,530)	< 0.001
Peak VL, Plasma^	46	9,100 (1,700, 26,300)	863 (355, 3,960)	0.003
Initial VL, Whole Blood^	43	35,200 (2,440, 23,700)	4,520 (779, 8,870)	0.004
Peak VL, Whole Blood^	46	35,200 (5,080, 101,000)	5,270 (1,210, 9,130)	0.002

HSCT Recipients	N	Symptomatic	Asymptomatic	P value
Initial VL, Plasma^	40	2,790 (1,530, 3,870)	466 (281, 954)	< 0.001
Peak VL, Plasma^	42	3,220 (1,570, 4,880)	825 (414, 1,900)	0.016
Initial VL, Whole Blood^	40	5,550 (1,740, 14,800)	5,130 (1,040, 8,250)	0.734
Peak VL, Whole Blood^	42	6,200 (1,740, 37,900)	5,350 (3,190, 15,000)	0.490

^ Median (Q1, Q3); K-W rank sum test

References

1. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant. *Am J Transplant.* 2013; 13(Suppl 4):93-106
2. Razonable R.R., Asberg A., Rollag J., et al. Virologic supression measured by a cytomegalovirus (CMV) DNA test calibrated to the World Health Organization International Standard Is predictive of CMV disease resolution in transplant recipients. *Clin Infect Dis* 2013; 56(11):1546-1553.