Safety and Efficacy of High-Dose Ganciclovir versus Standard Dosing for Cytomegalovirus Viremia in Solid Organ Transplant (SOT) Recipients

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The investigators declare no conflicts of interest

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Background

- Cytomegalovirus (CMV) infection is a common complication following solid organ transplantation (SOT)
- Standard dose ganciclovir (SD-GCV) for treatment of CMV infection/disease is 5 mg/kg every 12 hours
- High dose GCV (HD-GCV) [7.5-10 mg/kg BID, renally adjusted] has been suggested a potential option for GCV-resistant CMV infections, but data regarding safety and efficacy of this dosing strategy is limited

Study Objectives

Primary Objective: Compare incidence of hematologic adverse effects between SD-GCV and HD-GCV groups

Secondary Objectives:

- Compare between groups: Time to CMV viremia clearance, incidence of CMV disease progression, incidence of repeat CMV viremia within 30 days after stopping treatment, use of granulocyte colony stimulating factor (G-CSF) therapy
- Describe the number of UL97 tests ordered and resistant genes detected

Ganciclovir Dosing

- Only first course of therapy per patient for index admission evaluated for group inclusion
- Receipt of <5 days of HD-GCV evaluated as being in SD-GCV group

Creatinine Clearance (mL/min)	SD- GCV (mg/kg)	SD Dosing Interval (hours)	HD-GCV (mg/kg)	HD Dosing Interval (hours)
≥70	5	12	7.5-10	12
50-69	2.5	12	5	12
25-49	2.5	24	5	24
10-24	1.25	24	2.5	24
<10	1.25	3 times per week	2.5	3 times per week

Methods

Study Design: Single center, retrospective cohort study
Inclusion Criteria: Adult (≥ 18 years old) SOT recipients admitted to Cleveland Clinic Main Campus and received IV GCV for treatment of CMV viremia for ≥5 days from 1/1/2017 - 1/31/2019
Exclusion Criteria: Bone marrow transplant recipients, HIV patients, non-SOT immunocompromising conditions, patients receiving continuous renal replacement therapy

Results

Table 1: Baseline Characteristics

	SD-GCV (n= 74)	HD-GCV (n= 47)	*P*
Type of solid organ transplant, n(%)[a]			
Liver	34 (46.0)	17 (36.2)	0.289
Lung	15 (20.3)	8 (17.0)	0.657
Kidney	12 (16.2)	12 (25.5)	0.210
Heart	9 (12.1)	9 (19.1)	0.293
Small bowel	3 (4.1)	2 (4.3)	1.000
Multi-visceral	2 (2.7)	2 (4.3)	0.641
Other	1 (1.4)	0 (0)	1.000
CMV serology at time of transplant, n(%)[b]			0.129
D+/R-	41 (55.4)	33 (68.1)	
D+/R+	17 (23.0)	7 (14.9)	
D-/R+	13 (17.6)	3 (6.4)	
D-/R-	1 (1.4)	1 (2.1)	
Unknown	2 (2.7)	4 (8.5)	
Hospital length of stay, median (IQR), d	7 (4-30)	15 (6-22)	0.158
Induction regimen, n (%)			
None	23 (31.1)	7 (14.9)	0.044
Anti-thymocyte globulin	25 (33.8)	19 (40.4)	0.46
Alemtuzumab	5 (6.8)	2 (4.3)	0.705
Basiliximab	6 (8.1)	8 (17.0)	0.135
Steroid	13 (17.6)	8 (17.0)	0.94
Other	1 (1.4)	2 (4.3)	0.56
Neutropenia at baseline, n (%)	7 (9.4)	2 (4.2)	0.48
Leukopenia at baseline, n (%)	22 (29.7)	10 (21.3)	0.304
Thrombocytopenia at baseline, n (%)	30 (40.5)	21 (44.7)	0.653
Valganciclovir prior to admission, n (%)	26 (35.1)	14 (29.8)	0.558
Time from transplant to CMV viremia, median (IQR), d	155 (40-452)	197 (49-493)	0.5286
CMV viral load at presentation, median (range), IU/mL	4620 (1185-17574)	7770 (1135-81034)	0.254

Results

Table 2: Hematologic Adverse Events

	N	Events (%)	Log-rank *P* value	Freedom from outcome at Day 14 (%)	Univariate Hazard Ratio	Univariate *P* Value
Neutropenia			0.75	95.5 (90.7-100)	0.85 (0.31-2.34)	0.75
SD-GCV	67	10 (15)		97.8 (93.6-100)		
HD-GCV	45	6 (13)				
Leukopenia			0.97	77.4 (66.9-89.5)	1.02 (0.54-1.92)	0.96
SD-GCV	53	23 (43)		75.7 (63.0-90.8)		
HD-GCV	37	16 (43)				
Thrombocytopenia			0.60	78.6 (67.1-92.0)	1.26 (0.50-3.20)	0.62
SD-GCV	42	10 (24)		76.9 (62.3-95.0)		
HD-GCV	26	8 (31)				

Figure 1: Probability of persistent CMV viremia

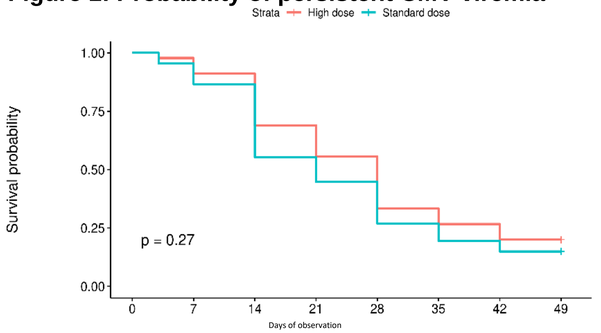

Table 3: Efficacy Analysis

- No difference in incidence of repeat CMV viremia after treatment (10 SD vs 11 HD, p= 0.098) or development of probable/proven CMV disease (26 SD vs 18 HD, p=0.724)

	SD-GCV (n=74)	HD-GCV (n=47)	*P* Value
G-CSF use, n (%)	18 (23.7)	7 (14.3)	0.295
Doses received, median (range)	2 (1-6)	5 (3-8)	**0.001**
CMV Antiviral Resistance test ordered, n (%)	15 (20.6)	20 (42.6)	**0.010**
Time from start of GCV therapy to test order, median (range), d	2 (1-8)	3 (2-106)	--
Resistance gene detected, n (%)	7 (46.7)	11 (55.0)	0.948
UL97 and UL54, n (%)	6/7	6/11	--
UL97 only, n (%)	1/7	3/11	--
UL54 only, n (%)	0/7	2/11	--

Discussion

- Observed no differences in incidence of leukopenia, neutropenia, or thrombocytopenia between strategies
  - HD-GCV group required more doses of G-CSF for immunological support, could provide possible explanation for no observed difference
- No difference in the likelihood or time to CMV viremia clearance or incidence of CMV disease
- Only 43% of HD-GCV patients had antiviral resistance testing conducted, 45% of which did not have resistance mutation detected
- Limitations:
  - Retrospective, single center study
    - Did not account for influence of concomitant medications on hematologic outcomes
    - Unable to account for patients who received SD-GCV prior to HD-GCV and additive effects on hematologic outcomes
- Despite limitations, if patients received doses higher than recommended by the package insert, regardless of intention, safety and efficacy of the treatment strategy was still able to be assessed

Conclusions

- HD-GCV did not demonstrate increased incidence of cytopenias compared to SD-GCV
- No observed difference in treatment efficacy between dosing strategies
- Opportunities exist for improving stewardship of antiviral resistance testing and use of G-CSF when considering HD-GCV therapy

References

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