Assessment of Cytomegalovirus Infections after Lung Transplantation in the Era of Extended Antiviral Prophylaxis

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Abstract

Background:

Cytomegalovirus (CMV) is the leading viral pathogen causing significant morbidity and mortality in lung transplant (LT) recipients. Antiviral prophylaxis has been extended to reduce its impact. This study describes the epidemiology and outcome of CMV in LT recipients before and after the implementation of prolonged antiviral prophylaxis.

Methods:

This study included all patients who received LT between Jan 2005 and Sept 2012. Previously, CMV D+/R- patients received 6 months while CMV R+ patients received 3 months of valganciclovir prophylaxis. In Jan 2007, the duration of prophylaxis was extended to 6 months for R+ and indefinitely for CMV D+ R- patients. Data before and after protocol implementation was collected. The causes and rate of compliance to CMV prophylaxis was assessed.

Results:

The study cohort included 107 LT recipients. Median follow up was 985 days. Median age at transplant was 58 (51.75-63) years. 50 recipients were male. The most common indications for LT were chronic obstructive pulmonary disease (32), idiopathic pulmonary fibrosis (32), and alpha 1 antitrypsin deficiency (10). Median duration of CMV prophylaxis was 136 days. 32 patients were CMV D+/R-. Asymptomatic CMV infection occurred in 10 patients, CMV disease in 9 patients, and recurrent CMV infection in 3 patients. Median time to onset of CMV infection was 378 days (262.5-658.5), and disease was 334 days (188-417). Most of the CMV infections (8/15) and disease (4/9) were observed after the implementation of prolonged prophylaxis. No impact of CMV on mortality was observed. 58 patients developed leukopenia, leading to temporary or permanent discontinuation of CMV prophylaxis in 23 cases.

Conclusion:

CMV infection and disease continue to occur in LT patients despite prolonged antiviral prophylaxis. Leukopenia was common during valganciclovir use. A safe and highly effective method for CMV prophylaxis remains elusive.

CMV Protocol

Due to concern for late CMV disease, change in CMV prophylaxis was implemented in January 2007

Prior to January 2007:

- CMV D+/R-: valganciclovir prophylaxis for 6 months
- CMV R+: valganciclovir prophylaxis for 3 months

After January 2007:

- CMV D+/R- : valganciclovir for at least 12 months (often given lifelong).
- CMV R+: valganciclovir prophylaxis for 6 months

Methods

- Reviewed all LT recipients from January 2005 until September 2012 for rate and compliance with CMV prophylaxis and rate of CMV infection and disease
- CMV infection- defined as presence of viremia without identified organ system involvement or symptoms
- CMV disease- defined as presence of CMV viremia in addition to symptoms of fever or CMV associated organ disease
  - CMV syndrome
  - Tissue invasive disease

Table 1: Patient Characteristics

Patient Characteristics (n=107)	Number (%), unless otherwise indicated
Age (mean, interquartile range)	**58 (51.75-63)**
Gender	
Female	57 (53.3%)
Male	50 (46.7%)
Underlying cause	
COPD	32 (29.9%)
Idiopathic Pulmonary Fibrosis	32 (29.9%)
Alpha 1 Antitrypsin Deficiency	10 (9.3%)
Cystic Fibrosis	5 (4.7%)
Sarcoidosis	3 (2.8%)
Connective Tissue Disease	6 (5.6%)
Interstitial Lung Disease, NOS	6 (5.6%)
Primary Pulmonary Hypertension	4 (3.7%)
Others	9 (8.4%)
Induction Immunosuppresion	
Muromonab-CD3- OKT3	44 (41.1%)
Antithymocyte globulin	35 (32.7%)
Others (did not receive OKT3/anti-thymocyte)	28 (26.2%)
CMV status	
CMV D+/R-	32 (29.9%)
CMV D+/R+	40 (37.4%)
CMV D-/R+	16(14.9%)
CMV D-/R-	19 (17.8%)
CMV Prophylaxis	
Ganciclovir (oral/IV)	6 (6.75%)
Valganciclovir	83 (93.25%)
Cytogam (additional)	4 (4.5%)
Transplant type	
Lung only	99 (92.5%)
Heart/Lung	5 (4.7%)
Liver/Lung	2 (1.9%)
Kidney/Lung	1 (0.9%)

Table 2: Results

Transplant 09/2005-01/2007	28 (26.2%)
Transplant 01/2007-09/2012	79 (73.8%)
CMV prior to extended prophylaxis	
CMV infection	7
CMV disease	5
CMV pneumonia	4
CMV colitis	1
BAL positivity only	3
CMV after extended prophylaxis	
CMV infection	8
CMV disease	4
CMV pneumonia	3
CMV colitis	2
CMV retinitis	1
Death	44 (41.1%)

Fig. 1: Leukopenia and Management

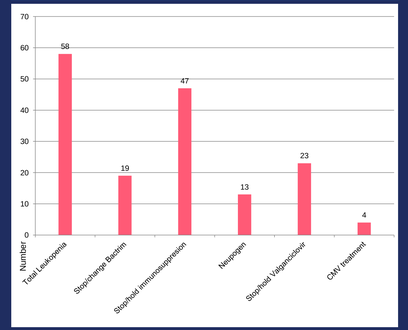

Table 3a: CMV Before Protocol Change

Case	Transplant Indication	CMV Status	CMV Prophylaxis & Duration (days)	CMV Disease	Outcome
1	Cystic Fibrosis	D+/R+	Ganciclovir (327)	Colitis, after prophylaxis	None
2	Emphysema	D-/R+	Valganiclovir (88)	Pneumonia, after prophylaxis	Viremia (twice)
3	IPF	D+/R-	Valganciclovir (361)	Pneumonia, after prophylaxis	None
4	Pulmonary fibrosis	D+/R+	Valganciclovir (84)	none	BAL positive , treated (twice)
5	IPF	D-/R+	Valganciclovir (93)	none	Viremia
6	Alpha 1 Antitrypsin	D+/R-	Valganciclovir+ Cytogam (359)	Pneumonia, after prophylaxis	Viremia
7	Emphysema	D+/R+	Valganciclovir (92)	none	Viremia
8	IPF	D+/R+	Valganciclovir (85)	Pneumonia, off prophylaxis	None

Table 3b: CMV After Protocol Change

9	Scleroderma-Fibrosis	D+/R-	Valganciclovir	**Pneumonia, on prophylaxis**	**Suspected Resist; Death**
10	IPF	D+/R+	Valganciclovir (111)	none	Viremia
11	Emphysema	D+/R+	valganciclovir (102)	none	Viremia (twice)
12	COPD	D-/R+	valganciclovir (90)	none	BAL positive, not treated
13	COPD	D+/R+	Valganciclovir (365)	none	Viremia
14	Emphysema	D+/R+	Valganciclovir (365)	none	**viremia on prophylaxis**
15	COPD	D+/R+	Valganciclovir (231)	none	Viremia
16	IPF	D+/R+	Valganciclovir (266)	none	Viremia
17	alpha 1 antitrypsin	D-/R+	Valganciclovir (906)	none	BAL positive, treated
18	Hypersn pneumonitis	D-/R+	Valganciclovir (182)	pneumonia, after prophylaxis	None
19	Cystic Fibrosis	D+/R-	Valganciclovir	**Pneumonia, colitis, retinitis, on prophylaxis**	**Confirmed Resistance**
20	IPF	D-/R+	Valganciclovir (183)	**Colitis, on prophylaxis**	None

Discussion

- The total number of CMV disease and infection appeared to decline following extended prophylaxis
- Two cases of CMV resistance (one confirmed, one suspected) were noted after extended prophylaxis
- Leukopenia is a common complication in LT patients. Standardized approach to management is required.

Conclusions

- CMV infection and disease continue to occur in LT patients despite prolonged antiviral prophylaxis. Leukopenia was common during valganciclovir use. A safe and highly effective method for CMV prophylaxis remains elusive.
- Cases of resistance were noted following extended prophylaxis, raising possibility of increasing rates of resistant CMV infections following increased exposure to antivirals