Burden of Cytomegalovirus Infection Among Allogeneic Hematopoietic Cell Transplant Recipients

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INTRODUCTION

- Patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) procedures are at increased risk of opportunistic infections, including double-stranded DNA (dsDNA) viral infections such as cytomegalovirus (CMV).[1]
- CMV infection may occur as early as the first 30 days post transplant in allo-HCT patients, regardless of whether nonmyeloablative or myeloablative conditioning regimens are used. However, patients who receive myeloablative conditioning regimens are at higher risk of high-grade viremia.[2]
- CMV infection is associated with numerous complications, most notably pneumonia, among allo-HCT recipients.[3]
- Even with active screening and preemptive therapy strategies that have minimized the progression to CMV disease in allo-HCT recipients, non-relapse mortality remains significant and is correlated with CMV viral load.[3-5]
- There are few data, especially using recent testing methodology, on the overall prevalence of CMV infections among allo-HCT recipients and the associated clinical burden.
- The objectives of this study were to examine the rates of CMV infection during hospitalization for allo-HCT and the impact of CMV infection on hospital length of stay (LOS), mortality, and hospital readmission rate.

METHODS

Study population

- Patients who received allo-HCT between January 2009 and September 2013 were identified from the Premier hospital database by an International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) code for allo-HCT on hospital discharge records. The first allo-HCT procedure was defined as the initial hospitalization event. Allo-HCT recipients were grouped into two study cohorts: patients with a documented CMV viral infection during their initial allo-HCT hospitalization and those without.

Demographics and clinical characteristics

- Demographics and clinical characteristics were evaluated using available records in the database during the initial hospitalizations and during the 12 months prior to hospitalization for allo-HCT.
  - Clinical characteristics included Charlson Comorbidity Index (CCI) score and All Patient Refined Diagnosis Related Group (APR-DRG) severity of illness level.
    - The CCI is a method used commonly to assess the overall comorbidity levels of patients. It is a weighted score based on the diagnosis of 19 specific diseases.
    - APR-DRG is a method designed to categorize patients into similar disease categories and to identify them by severity level. There are four different levels of severity: Level 1–Minor, Level 2–Moderate, Level 3–Major, Level 4–Extreme.

Outcome measurements

- Mean LOS for allo-HCT hospitalizations was evaluated using hospital discharge records and compared among study cohorts.
- Mortality rates during initial allo-HCT hospitalization and during hospital readmission up to a 12-month follow-up period were evaluated and compared among study cohorts.
- Rates of hospital readmissions for any cause and those specifically involving dsDNA viral infections up to a 12-month follow-up period were evaluated and compared among study cohorts.
  - dsDNA viral infections were categorized as the following:
    - any dsDNA viral infection
      - CMV infection
      - BK virus infection
      - adenovirus (AdV) infection
      - other dsDNA viral infection
        - human papilloma virus (HPV), human herpesvirus (HHV) 6 or 7, varicella zoster virus (VZV), Epstein–Barr virus (EBV), and herpes simplex virus (HSV).

RESULTS

- As identified by ICD-9-CM codes, 110/1617 (6.8%; mean age: 35.4 years) of the study population had a CMV infection during their initial allo-HCT hospitalization (**Table 1**).
- Most patients in both cohorts had a relatively low number of comorbidities, with CCI = 0–2 (0–2 comorbidities in the CCI list) (**Table 2**).
- The percentage of patients with major and extreme illness severity levels, as indicated by APR-DRG, was greater among patients with CMV infections than those without (87.3% vs. 33.5%, p<0.0001) (**Table 2**).
- The mean LOS per patient during the initial allo-HCT hospitalization was significantly greater among patients with CMV viral infection versus those without (59.2 ± [standard deviation] 34.5 days vs. 32.6 ± 21.2 days, p<0.0001) (**Figure 1**).
- A significantly higher percentage of patients died among those who had CMV infection during initial allo-HCT hospitalization compared with patients who did not (21.8% vs. 6.2%, p<0.0001) (**Figure 2**).
- During hospital readmissions over the next 12 months, the mortality rate tended to be higher among those who had CMV infection during initial allo-HCT hospitalization compared with patients who did not (22.1% vs. 14.4%, p=0.0527) (**Figure 2**).
- Over the next 12 months, rates of hospital readmissions for any cause among patients alive after initial allo-HCT hospitalization were similar in patients with and without CMV infection during initial allo-HCT hospitalizations (59.3% and 59.6%, respectively [p=0.9580]).
  - A greater percentage of patients with CMV infection during initial allo-HCT hospitalization than without infection were readmitted to hospital for CMV infection within a 12-month follow-up period (23.3% vs. 12.6%, p=0.0046) (**Figure 3**).

Table 1. Patient demographics

Factor	Number of patients			
CMV infection in initial allo-HCT hospitalization	**No N=1507**		**Yes N=110**	
Age (years)				
Mean (SD)	43.0 (20.4)		35.4 (23.1)	
Median	49		37	
	n	**%**	**n**	**%**
Adults/children				
Adult (≥18 years old)	1253	83.2	75	68.2
Child (<18 years old)	254	16.9	35	31.8
Sex				
Female	653	43.3	43	39.1
Male	854	56.7	67	60.9
US region				
Midwest	127	8.4	6	5.5
Northeast	843	55.9	66	60.0
South	516	34.2	38	34.6
West	21	1.4	0	0.0
Race/ethnicity				
White	974	64.6	52	47.3
Black	164	10.9	15	13.6
Hispanic	32	2.1	5	4.6
Other	337	22.4	38	34.6
Health plan				
Commercial-Managed Care	979	65.0	67	60.9
Medicaid	254	16.9	28	25.5
Medicare	199	13.2	9	8.2
Others	75	5.0	6	5.5
Urban/rural hospital				
Rural	85	5.6	7	6.4
Urban	1422	94.4	103	93.6
Teaching hospital				
No	52	3.5	5	4.6
Yes	1455	96.6	105	95.5
Number of beds				
<200	118	7.8	9	8.2
200–399	135	9.0	5	4.6
400–599	167	11.1	13	11.8
≥600	1087	72.1	83	75.5

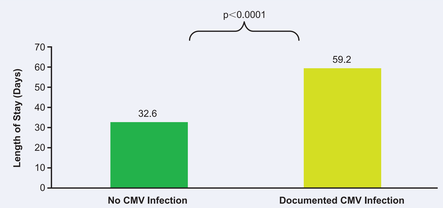
Allo-HCT, allogeneic hematopoietic cell transplantation; CMV, cytomegalovirus; SD, standard deviation.

Table 2. Clinical characteristics of patients

Factor	Number of patients				
Documented CMV infection in initial allo-HCT hospitalization	**No N=1507**		**Yes N=110**		**p value**
CCI					
Mean (SD)	2.3 (1.6)		2.4 (1.7)		0.3516
Median	2		2		
	n	**%**	**n**	**%**	
CCI group					0.1947
0	238	15.8	19	17.3	
1–2	784	52.0	46	41.8	
3–4	379	25.2	36	32.7	
≥5	106	7.0	9	8.2	
APR-DRG severity level					<0.0001
1–Minor	466	30.9	0	0.0	
2–Moderate	537	35.6	14	12.7	
3–Major	239	15.9	24	21.8	
4–Extreme	265	17.6	72	65.5	

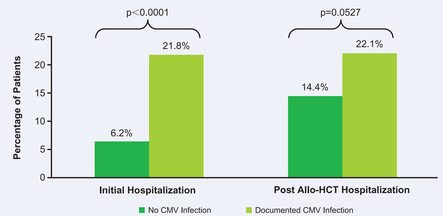
Allo-HCT, allogeneic hematopoietic cell transplantation; APR-DRG, All Patient Refined Diagnosis Related Group; CCI, Charlson Comorbidity Index; CMV, cytomegalovirus; SD, standard deviation.

Figure 1. Initial allogeneic hematopoietic cell transplantation hospitalization mean length of stay



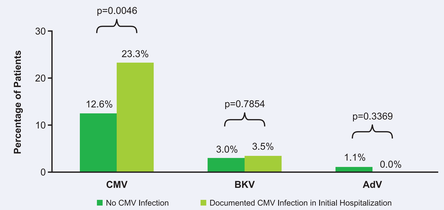
CMV, cytomegalovirus

Figure 2. Inpatient mortality during initial hospital admission and in hospital readmissions evaluated for up to 12 months post-discharge for allogeneic hematopoietic cell transplantation (allo-HCT) hospitalization



CMV, cytomegalovirus

Figure 3. Documented double-stranded DNA viral infections in patients with and without cytomegalovirus (CMV) infection at initial hospitalization in the 12 months post-discharge for allogeneic hematopoietic cell transplantation hospitalization



AdV, adenovirus; BKV, BK virus

LIMITATIONS

- Identification of CMV infections was based on hospital discharge ICD-9-CM diagnosis codes, and therefore it is likely that only patients with more severe infections were identified. Thus, the CMV infection rates estimated in this study may represent a potential underestimate of the prevalence rates of such conditions.
- While the Premier hospital database contains information from a large number of hospitals across the US, it may not be representative of all types of transplant centers. In this study approximately three-quarters of allo-HCT recipients received their transplant in large hospitals (≥600 beds). Thus, the study findings may not be representative of all allo-HCT transplant recipients, especially among those who had allo-HCT in smaller hospitals.

CONCLUSIONS

- **In this large cohort of allo-HCT recipients, those who had documented CMV infections during their initial allo-HCT hospitalization had a hospital stay almost twice as long and had 3.5 times higher mortality during hospitalization than patients who did not.**
- **Because this cohort included those allo-HCT recipients who were CMV seronegative and thus at lower risk of CMV reactivation, the overall impact of CMV infections is likely to be underestimated in this study.**
- **Patients who had CMV infection during their initial allo-HCT hospitalization were more likely to be readmitted to the hospital for CMV infection recurrence.**

REFERENCES

1. Lin R and Liu Q. *J Hematol Oncol* 2013;6:94.
2. Nakamae H, et al. *Biol Blood Marrow Transplant* 2009;15:694–703.
3. Ljungman P, et al. *Hematol Oncol Clin North Am* 2011;25:151–169.
4. Liu J, et al. *Clin Microbiol Infect* 2015;21:1121.e9-e15.
5. Green ML, et al. Poster presented at 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 5–9, 2014, Washington, DC.

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DISCLOSURES

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