Double-Stranded DNA Virus Infections Among Allogeneic Hematopoietic Cell Transplant Recipients: Impact on Patient Survival and Hospital Resource Utilization

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INTRODUCTION

- Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for certain malignant and non-malignant hematologic diseases.[1]
- Immunosuppression puts allo-HCT recipients at increased risk for opportunistic infections, including double-stranded DNA (dsDNA) viral infections.[2]
- dsDNA viral infections, such as those with cytomegalovirus (CMV), adenovirus (AdV), and varicella zoster virus (VZV), are of particular concern among allo-HCT recipients, as they can be associated with severe complications including pneumonia, enteritis, hepatitis, and death.[3]
- There are few data, especially using recent testing methodology, on the overall prevalence of dsDNA viral infections among allo-HCT recipients.
- The objectives of this study were to evaluate the rates of dsDNA viral infections during hospitalization for allo-HCT and the impact of these infections on hospital resource utilization, hospital cost, and mortality.

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 dsDNA 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

- Rates of dsDNA viral infections (i.e., percentages of study cohorts), documented by diagnostic codes, were determined for the initial allo-HCT hospitalizations among study cohorts and compared. Documented dsDNA viral infections were categorized as the following:
  - any dsDNA viral infection
    - CMV infection
    - BK virus infection
    - AdV infection
    - human papilloma virus (HPV) infection
    - human herpes virus (HHV) 6 or 7 infection
    - VZV infection
    - Epstein–Barr virus (EBV) infection
    - herpes simplex virus (HSV) infection.
- Hospital resource utilization in terms of hospital length of stay (LOS) and costs associated with the hospitalization for allo-HCT were evaluated using hospital discharge records.
  - Hospital resource utilization was grouped into the following hospital departments based on the hospitalization records:
    - pharmacy department
    - room and board
    - laboratory tests
    - blood bank services.
- Mortality rates during initial allo-HCT hospitalizations were determined and compared among study cohorts.

RESULTS

- As identified by ICD-9-CM codes, 216/1671 (13.4%; mean age: 35.0 years) of the study population had a dsDNA viral infection during their initial allo-HCT hospitalization (**Table 1**).

Table 1. Patient demographics

Factor	Number of patients			
dsDNA viral infection in initial allo-HCT hospitalization	No N=1401		Yes N=216	
Age (years)				
Mean (SD)	43.7 (20.3)		35.0 (22.0)	
Median	49		38	
	n	%	n	%
Adults/children				
Adult (≥18 years)	1180	84.2	148	68.5
Child (<18 years)	221	15.8	68	31.5
Sex				
Female	613	43.8	83	38.4
Male	788	56.3	133	61.6
US region				
Midwest	119	8.5	14	6.5
Northeast	792	56.5	117	54.2
South	474	33.8	80	37.0
West	16	1.1	5	2.3
Race/ethnicity				
White	906	64.7	120	55.6
Black	152	10.9	27	12.5
Hispanic	29	2.1	8	3.7
Other	314	22.4	61	28.2
Health plan				
Commercial-Managed Care	908	64.8	138	63.9
Medicaid	236	16.9	46	21.3
Medicare	196	14.0	12	5.6
Others	61	4.4	20	9.3
Urban/rural hospital				
Rural	77	5.5	15	6.9
Urban	1324	94.5	201	93.1
Teaching hospital				
No	50	3.6	7	3.2
Yes	1351	96.4	209	96.8
Number of beds				
<200	109	7.8	18	8.3
200–399	127	9.1	13	6.0
400–599	155	11.1	25	11.6
≥600	1010	72.1	160	74.1

Allo-HCT, allogeneic hematopoietic cell transplantation; dsDNA, double-stranded DNA; SD, standard deviation.

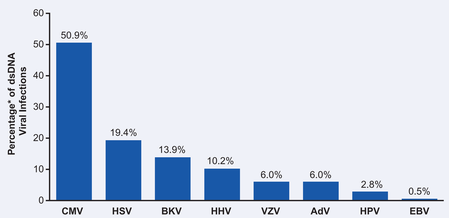
Table 2. Clinical characteristics of patients

Factor	Number of patients				
Documented dsDNA viral infection in initial allo-HCT hospitalization	No N=1401		Yes N=216		p value
CCI					
Mean (SD)	2.3 (1.6)		2.4 (1.8)		0.4709
Median	2		2		
	n	%	n	%	
CCI group					0.2315
0	220	15.7	37	17.1	
1–2	733	52.3	97	44.9	
3–4	351	25.1	64	29.6	
≥5	97	6.9	18	8.3	
APR-DRG severity level					<0.0001
1–Minor	459	32.8	7	3.2	
2–Moderate	505	36.1	46	21.3	
3–Major	208	14.8	55	25.5	
4–Extreme	229	16.4	108	50.0	

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

- 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 dsDNA viral infections than those without (75.5% vs. 31.2%, p<0.0001) (**Table 2**).
- Among patients with documented dsDNA viral infections during initial allo-HCT hospitalizations, the most frequent viral infections were CMV (50.9%), HSV (19.4%), and BK virus (13.9%) (**Figure 1**).
- The mean LOS per patient for the initial allo-HCT hospitalization was significantly greater among patients with dsDNA viral infections versus those without (53.2 ± [standard deviation] 31.9 days vs. 31.5 ± 20.2 days, p<0.0001) (**Figure 2**).
- Total initial allo-HCT hospitalization costs per patient were higher among patients with dsDNA viral infections versus those without (median [interquartile range]: $211,019 [$145,578–$328,501] vs. $125,857 [$79,989–$183,269]) (**Figure 3**).

Figure 1. Percentage of patients with different double-stranded DNA (dsDNA) viral infections during initial allogeneic hematopoietic cell transplantation hospitalization



*Percentages are calculated as the number of patients with each type of dsDNA viral infection divided by the total number of patients with any dsDNA viral infections (n=216). Patients may have more than one type of dsDNA viral infection and thus the sum of the percentages may be greater than 100%.
AdV, adenovirus; BKV, BK virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpes virus; HPV, human papilloma virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Figure 2. Mean length of hospital stay in patients with and without documented double-stranded DNA (dsDNA) viral infections during initial allogeneic hematopoietic cell transplantation hospitalizations

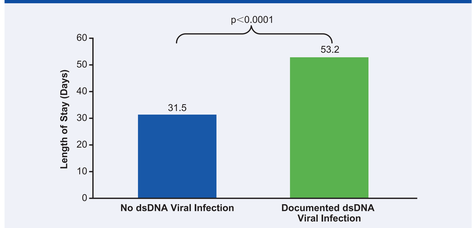
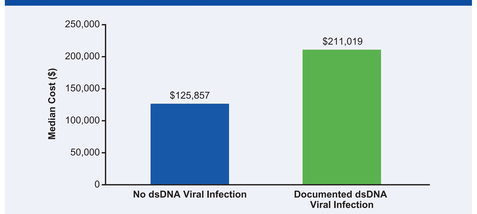


Figure 3. Total hospitalization costs in patients with and without documented double-stranded DNA (dsDNA) viral infections during initial allogeneic hematopoietic cell transplantation hospitalization



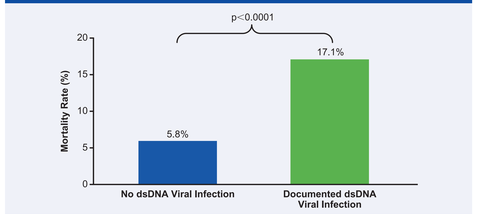
- Hospitalization costs of allo-HCT recipients with and without dsDNA viral infections during allo-HCT hospitalizations for the pharmacy department were $62,418 ($38,083–$116,092) versus $34,913 ($22,017–$55,824); for room and board were $60,674 ($21,764–$110,874) versus $36,313 ($25,540–$61,992); for laboratory tests were $34,884 ($17,904–$78,574) versus $13,270 ($6,746–$35,293); and for blood bank services were $19,743 ($3,046–$18,236) versus $7,384 ($8,491–$53,663) (**Table 3**).
- A significantly higher percentage of patients with a dsDNA viral infection died during the initial allo-HCT hospitalization compared with patients without a dsDNA viral infection (17.1% vs. 5.8%, p<0.0001) (**Figure 4**).

Table 3. Initial allogeneic hematopoietic cell transplantation (allo-HCT) hospitalization costs for selected hospital departments

	Documented dsDNA viral infection in initial allo-HCT hospitalization	
Hospital department	No N=1401	Yes N=216
Pharmacy ($)	34,913	62,418
Room and board ($)	36,313	60,674
Laboratory tests ($)	13,270	34,884
Blood bank services ($)	7,384	19,743

Values are median costs.
dsDNA, double-stranded DNA.

Figure 4. Mortality rates in patients with and without documented double-stranded DNA (dsDNA) viral infections during initial allogeneic hematopoietic cell transplantation hospitalizations



LIMITATIONS

Identification of dsDNA viral infections were 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 dsDNA viral infection rates estimated in this study may represent an 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

- **Reported dsDNA viral infections among allo-HCT recipients were associated with significant hospital resource use and hospital costs.**
- **Moreover, allo-HCT recipients with documented dsDNA viral infections had nearly a 3-fold higher mortality rate during the initial hospitalization in comparison to those without such diagnoses.**

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ACKNOWLEDGMENTS

Study supported by Chimerix, Durham, NC. Editorial assistance was provided by Andrew Shepherd and Katrina Rimmer of Caudex, UK, and was supported by Chimerix, Durham, NC.

DISCLOSURES

This study was supported by Chimerix, Durham, NC. EM is an employee of Chimerix, Durham, NC. JL and ML-S are employees of Novosys Health, which received support from Chimerix, Durham, NC, for conducting this study and development of this poster.