Prevalence of Double-Stranded DNA Viral Infections Among Allogeneic Hematopoietic Cell Transplant Recipients

Essy Mozaffari,[1] PharmD, MPH, MBA; Jay Lin,[2] PhD, MBA; Melissa Lingohr-Smith,[2] PhD

[1]Chimerix, Inc., Durham, NC, [2]Novosys Health, Green Brook, NJ

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Presenting author contact details
E Mozaffari
Chimerix Inc.
2505 Meridian Pkwy, Suite 340
Durham, NC 27713
Tel: (919) 806-1074
Fax: (919) 806-1146
email: emozaffari@chimerix.com

ABSTRACT

Background: Viral infections remain a leading cause of morbidity and non-relapse mortality following allogeneic hematopoietic cell transplant (allo-HCT). In this study we evaluated the prevalence of double stranded (ds) DNA viral infections post allo-HCT using hospital discharge records.

Methods: Patients who received an allo-HCT between January 2009 and September 2013 were identified from the Premier Hospital database using ICD-9-CM codes. The first allo-HCT procedure was defined as the index event. The frequencies of opportunistic infections, documented by diagnostic codes, were evaluated during the index hospitalization and 12 months after the index allo-HCT hospitalization.

Results: Of patients who received allo-HCT (N=1617; mean age: 42.5 years) 57.0% were male and 17.9% were ≤18 years of age. Most patients received allo-HCT in urban (94.3%), large (≥600 beds: 72.4%), teaching hospitals (96.5%). During the index hospitalization, 851 patients (52.6%) had a diagnostic code for opportunistic infection in their discharge records, and 13.4% (n=216) had dsDNA viral infections. Among patients with dsDNA viral infections during the index hospitalization, 50.9% (n=110) had infections of cytomegalovirus (CMV), 13.9% (n=30) BK virus, 6.0% (n=13) adenovirus (AdV), and 38.0% (n=82) had other dsDNA viral infections (VZV, Herpes, HPV, EBV). Among the patients who survived the index allo-HCT hospitalization (n=1,499), 45.6% (n=683) had a diagnostic code for opportunistic infection and 18.2% (n=273) had dsDNA viral infections. Among patients with dsDNA viral infections among patients who survived the index allo-HCT hospitalization, 72.5% (n=198) had infections with CMV, 16.5% (n=45) BK virus, 5.5% (n=15) AdV, and 27.1% (n=74) had other dsDNA viral infections.

Conclusion: Based on analysis of hospital discharge records, about 3 out of every 4 allo-HCT recipients in this study population had an opportunistic infection during the first year post allo-HCT; this estimate is conservative due to potential undercoding. One out of every 3 opportunistic infections was a dsDNA viral infection. Although antimicrobials are initiated post allo-HCT to prevent opportunistic bacterial and fungal infections, the toxicities of current antiviral drugs do not allow their use for routine prevention of viral infections among these severely immunocompromised patients.

INTRODUCTION

- Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for certain malignant and non-malignant diseases.[1]
- Immunosuppressive therapy is required as part of the allo-HCT procedure in order to avoid graft rejection and graft-versus-host disease (GVHD), which are major causes of morbidity and mortality among recipients of allo-HCT.[2]
- Immunosuppressive therapy puts allo-HCT recipients at increased risk for opportunistic infections, including double-stranded DNA (dsDNA) viral infections.[3]
- dsDNA viral infections, such as those with cytomegalovirus (CMV), adenovirus (AdV), and varicella zoster virus (VZV), are of particular concern among HCT recipients, as they can be associated with severe complications including pneumonia, enteritis, hepatitis, and death.[4]
- There are few data, especially those based on recent testing methodology, on the overall prevalence of dsDNA viral infections among allo-HCT recipients.

OBJECTIVES

The objectives of this study were to evaluate the prevalence of opportunistic infections, including dsDNA viral infections, during allo-HCT hospitalizations using hospital discharge records and to examine the frequency of post allo-HCT hospital readmissions and their causes.

METHODS

Study population

Patients who received an allo-HCT between January 2009 and September 2013 were identified from the Premier Hospital database based on having an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for allo-HCT. The first allo-HCT procedure was defined as the index event.

Demographics and clinical characteristics

Demographics, including age, sex, US region of residence, race, health plan type, urban/rural hospital, hospital teaching status, and hospital size, and clinical characteristics, including Charlson Comorbidity Index (CCI) score and All Patient Refined Diagnosis Related Group (APR-DRG) severity of illness level were evaluated during a 12-month baseline period.

- The CCI is a commonly used method of estimating the 1-year mortality for a patient with certain comorbid conditions. It is a weighted score based on the occurrence of 19 specific diseases diagnosed during the baseline period prior to the index date, as well as on the index date.
- APR-DRG is a methodology designed to categorize patients into similar disease categories and to identify them by severity level. There are 4 different levels of severity: Level 1–Minor, Level 2–Moderate, Level 3–Major, Level 4–Extreme.

Outcome measurements

The frequencies of opportunistic infections, documented by diagnostic codes, were evaluated during the index hospitalization and 12 months after the index allo-HCT hospitalization. Opportunistic infections were categorized as follows:

- Any opportunistic infection, including fungal, bacterial, and virus infections
- dsDNA viral infection
  - CMV infection
  - BK virus infection
  - AdV infection
  - Other dsDNA virus infections, including human papilloma virus (HPV), human herpes virus (HHV) 6 or 7, VZV, Epstein-Barr virus (EBV), and herpes simplex virus (HSV)

The frequency and causes for hospital readmissions were evaluated during a 12-month follow-up period after the allo-HCT index hospitalization using hospital discharge records. The causes of hospital readmissions were categorized as follows:

- Readmission for any cause
- Any opportunistic infection-related readmission
- dsDNA virus-related readmission
  - CMV-related readmission
  - BK virus-related readmission
  - Other dsDNA virus-related readmission
- GVHD-related readmission
- Neutropenia-related readmission
- Renal impairment-related readmission

RESULTS

- The demographic and clinical characteristics of patients in the study cohort are described in **Tables 1** and **2**:
  - Of patients who received allo-HCT (n=1617; mean age: 42.5 years), 57.0% were male and 17.9% were ≤18 years of age (**Table 1**).
  - The majority (51.3%) of patients who received allo-HCT had CCI = 1–2. The proportions of patients with APR-DRG illness severity levels 1, 2, 3, and 4 were 28.8%, 34.1%, 16.3%, and 20.8%, respectively (**Table 2**).
- During the index hospitalization, 52.6% of patients (n=851) had a diagnostic code for opportunistic infection in their discharge records.
- During the index hospitalization, 13.4% of patients (n=216) had a diagnostic code for dsDNA viral infections, and 27.8% of patients (n=449) had a diagnosis of dsDNA viral infection during the index hospitalization or during readmission hospitalizations within 12 months from the index hospitalization.
- Among patients with dsDNA viral infections, CMV, BK virus, and AdV comprised 50.9% (n=110), 13.9% (n=30), and 6.0% (n=13) of these infections, while 38.0% of patients (n=82) had other dsDNA viral infections (HPV, HHV, VZV, EBV, and HSV).
- During index allo-HCT hospitalizations, 118 deaths occurred, resulting in a population of 1499 alive post-discharge patients.
- Of the 216 patients with dsDNA viral infections, 17.1% (n=37) died during the index hospitalization. In comparison, among 1401 patients without dsDNA viral infections, 5.8% (n=81) died during the index hospitalization ($p<0.0001$).
- Among the patients who survived the index allo-HCT hospitalization, 45.6% (n=683) of hospital readmissions were related to opportunistic infections (including dsDNA or other infections) and 18.2% (n=273) were related to dsDNA viral infections during the follow-up period.
- Among the 179 patients with dsDNA viral infections during the index hospitalization who survived, 45.8% (n=82) and 22.4% (n=40) of hospital readmissions were related to opportunistic infections and dsDNA viral infections, respectively, during the follow-up period.
- Of the hospital readmissions related to dsDNA viral infections (n=273), 72.5% (n=198) were for CMV, 16.5% (n=45) were for BK virus, 5.5% (n=15) were for AdV, and 27.1% (n=74) were for other dsDNA viral infections.
- Among patients with dsDNA viral infections during the index hospitalization or during readmission hospitalizations within 12 months from the index hospitalization (N=449), 64.1% (n=288) were for CMV, 16.0% (n=72) were for BK virus, 6.2% (n=28) were for AdV, and 32.3% (n=145) were for other dsDNA viral infections (**Figure 1**).

Table 1. Demographics of Study Population with Allo-HCT

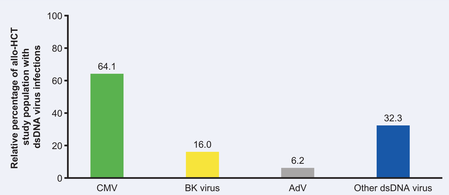
Demographic	Allogeneic HCT N=1617	
Age (years)		
N	1617	
Mean	42.5	
Standard deviation	20.7	
Median	48	
	n	**%**
Age Group		
0–20 years	325	20.1
21–40 years	297	18.4
41–50 years	262	16.2
51–60 years	367	22.7
≥61 years	366	22.6
Adult/Pediatric		
Adult (≥18 years old)	1328	82.1
Pediatric (<18 years old)	289	17.9
Sex		
Female	696	43.0
Male	921	57.0
US Region		
Midwest	133	8.2
Northeast	909	56.2
South	554	34.3
West	21	1.3
Race/Ethnicity		
Black	179	11.1
Hispanic	37	2.3
Other	375	23.2
White	1026	63.4
Urban/Rural Hospital		
Rural	92	5.7
Urban	1525	94.3
Teaching Status		
No	57	3.5
Yes	1560	96.5
Number of Beds		
<200	127	7.8
200–399	140	8.7
400–599	180	11.1
≥600	1170	72.4

Table 2. Clinical Characteristics of Study Population with Allo-HCT

Clinical Characteristic		
Charlson Comorbidity Index (CCI)		
N	1617	
Mean	2.3	
Standard deviation	1.7	
Median	2.0	
	n	**%**
CCI Group		
0	257	15.9
1–2	830	51.3
3–4	415	25.7
≥5	115	7.1
APR-DRG Severity Level		
1–Minor	466	28.8
2–Moderate	551	34.1
3–Major	263	16.3
4–Extreme	337	20.8

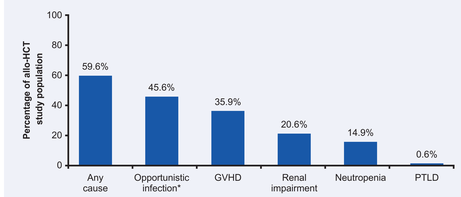
All Patient Refined Diagnosis Related Group (APR-DRG)

Figure 1. Relative Percentage of dsDNA Viral Infections Grouped by Virus Type During the Index Hospitalization and Follow-up Period among Patients with Allo-HCT with dsDNA Viral Infections (N=449)



AdV: adenovirus; CMV: cytomegalovirus. HCT: hematopoietic cell transplantation. Other dsDNA viral infections included those of human papilloma virus, human herpes virus 6 or 7, varicella zoster virus, Epstein-Barr virus, and herpes simplex virus

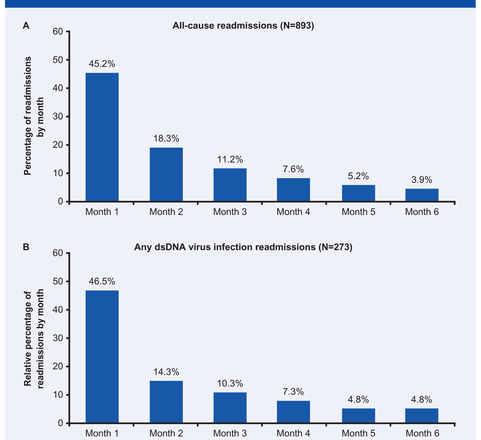
Figure 2. Frequency of Hospital Readmissions Categorized by Cause (N=1617)



*Opportunistic infection related readmissions include readmissions related to viral, bacterial, and fungal infections. Patients may have multiple readmissions or readmission with multiple diagnoses. Thus, the categories of readmissions are not mutually exclusive. GVHD: graft-versus-host disease; PTLD: post-transplant lymphoproliferative disorder

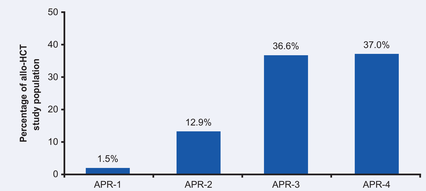
- Among the patients who survived the index allo-HCT hospitalization, 59.6% (n=893) had a hospital readmission for any cause during the 12 months post allo-HCT hospitalization (**Figure 2**).
  - Approximately 3 out of 4 (45.6%/59.6%) readmissions involved an opportunistic infection (**Figure 2**).
  - Hospital readmissions were most frequently related to opportunistic infections (45.6%, n=683), followed by GVHD (35.9%, n=538), renal impairment (20.6%, n=309), and dsDNA viral infections (18.2%, n=273) (**Figure 2**). The frequencies of hospital readmissions related to opportunistic infections and dsDNA viral infections are not mutually exclusive, as patients may have had both dsDNA and other non-dsDNA opportunistic infections.
- Of the hospital readmissions for any cause, 45.2% occurred within 1 month and 74.7% occurred within the first 3 months (**Figure 3A**).
- Among patients with dsDNA viral infections during the index hospitalization who had dsDNA viral readmissions, 46.5% occurred within 1 month and 71.1% occurred within the first 3 months (**Figure 3B**).
- Hospital readmissions of patients with high severity APR-DRG levels of 3–major severity (36.6%) and 4–extreme severity (37.0%) were most frequent during the follow-up period (**Figure 4**).
- Among allo-HCT patients in this study population, 73.2% (n=1184) of hospital discharges had a diagnostic code for an opportunistic infection during either the index hospitalization or the first year post allo-HCT.

Figure 3. Relative Percentage* of Monthly Hospital Readmissions Related to A) All Causes and B) Any dsDNA Viral Infection Readmissions, for Months 1–6 of the Follow-up Period



*Relative percentage refers to the percentage of hospital readmissions among patients with such related readmissions in the follow-up period

Figure 4. Frequency of Hospital Readmissions Categorized by All Patient Refined Diagnosis Related Group (APR-DRG) Severity of Illness Level (N=893)



Severity of illness level rated 1–4: minor, moderate, major, and extreme

LIMITATIONS

Patients with viral infections were identified using ICD-9-CM diagnosis codes in the study; those with less severe viral infections might not have been coded with the ICD-9-CM diagnosis codes during hospitalization. Thus, the prevalence of viral infections may have been underestimated in this study. Patients with other disease conditions identified by ICD-9-CM diagnosis codes can also be subject to undercoding.

CONCLUSIONS

- **Based on analysis of hospital discharge records, approximately 3 out of every 4 hospitalizations of allo-HCT recipients in this study population involved an opportunistic infection within the first year post allo-HCT. This estimate is conservative because of potential undercoding of infections in such patients.**
- **Approximately 1 out of every 3 opportunistic infections was a dsDNA viral infection.**
- **Over half of the patients who received allo-HCT had at least 1 hospitalization in the 12 months following allo-HCT, and more than two-thirds of the patients hospitalized were classified as "major" and "extreme" in terms of severity level. Patients with dsDNA virus infections at index hospitalization had a higher mortality rate than patients without dsDNA virus infections.**
- **These results support that allo-HCT recipients are at risk of complications during the first few months after transplantation until reconstitution of their immune system function, with nearly half of hospital readmissions observed to be related to infections.**
- **Although antimicrobials are initiated post allo-HCT to prevent opportunistic bacterial and fungal infections, the toxicities of current antiviral drugs[5] do not allow their use for routine prevention of viral infections among these severely immunocompromised patients.**

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DISCLOSURES

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