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Outcomes of Influenza Infections in Hematopoietic Cell Transplant Recipients: Application of an Immunodeficiency Scoring Index

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A B S T R A C T

Hematopoietic cell transplant (HCT) recipients have lower immune response to influenza vaccination and are susceptible to lower respiratory tract infection (LRI) and death. We determined clinical characteristics and outcomes of laboratory-confirmed influenza, including 2014/H3N2 infection, in 146 HCT recipients. An immunodeficiency scoring index (ISI) was applied to identify patients at high risk for LRI and death. Thirty-three patients (23%) developed LRI and 7 (5%) died within 30 days of diagnosis. Most patients received antiviral therapy (83%); however, only 18% received it within 48 hours of symptom onset. The incidence of LRI was significantly higher in the ISI high-risk group than it was in the low-risk group ($P < .001$). Receiving early antiviral therapy was associated with a substantial reduction in LRI for all ISI risk groups with the greatest risk reduction observed in the high-risk group. When compared with previous seasons, no significant differences in patient outcomes were observed during the 2014/H3N2 season; however, antiviral therapy was more promptly initiated in the latter season. The ISI that was originally developed for respiratory syncytial virus may help identify HCT recipients at risk for progression to LRI and mortality after influenza infection. These patients should be monitored more closely. Early initiation of antiviral therapy for influenza in HCT recipients, regardless of the ISI risk group, may improve morbidity as well as mortality.

INTRODUCTION

The severity of influenza infection in the general population depends on vaccination uptake and the main circulating virus, among other factors. Some seasons, such as the 2009/H1N1 pandemic season, have had higher rates of hospitalizations (274,000 hospitalizations in the United States alone); however, disease severity in that season was not significantly different from that in previous seasons [1,2]. The severity of influenza infection also depends on the host immune status and its underlying risk factors. Multiple studies have shown that susceptible populations, such as children, the elderly, pregnant women, solid-organ transplant recipients, and hematopoietic cell transplant (HCT) recipients, have higher risk of developing severe disease and higher rates of complications, such as hospitalizations, prolonged viral shedding, emergence of viral resistance, and mortality, than the general population [3-7].

Influenza infection in HCT recipients has been increasingly recognized as a serious infection with severe implications [8-10]. In fact, it is 1 of the most common respiratory viral infections (influenza accounts for 30% of all respiratory viral infections) and it causes increased morbidity and mortality in this population. Up to 35% of these patients progress to lower respiratory tract infection (LRI) with subsequent high mortality [10,11]. Previous studies have revealed various risk factors for influenza-associated LRI in HCT recipients, such as lymphocytopenia, nosocomial acquisition of the virus, older age, and pre-existing lung disease [12-14]. Using these clinically available risk factors, an immunodeficiency scoring index (ISI) was developed in HCT recipients with respiratory syncytial virus (RSV) infections to help identify patients at higher risk for complications and those who would benefit the most from antiviral therapy [15]. As this

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Table 1
Clinical Characteristics and Outcomes of Influenza Infections in 146 HCT Recipients (N = 146)

Characteristic	Value
Age, median (range), yr	52 (14-80)
Sex	
Male	77 (53)
Female	69 (47)
Race	
Non-Hispanic white	87 (60)
Black	17 (12)
Hispanic	34 (23)
Other	8 (5)
Donor relationship	
Matched related	50 (34)
Matched unrelated	34 (23)
Mismatched	10 (7)
Autologous	52 (36)
HCT cell source	
Peripheral	111 (76)
Marrow	29 (20)
Cord	2 (1)
Time from HCT to infection	
Median (range), d	398 (2-7140)
Acute GVHD	11 (8)
Chronic GVHD	27 (18)
Underlying malignancy	
Leukemia	69 (47)
Lymphoma	29 (20)
Other	48 (33)
Cancer status at the time of infection	
Remission	115 (79)
Active/relapse	31 (21)
Myeloablative conditioning regimen (past 100 days)	17 (12)
Corticosteroids within 30 days of diagnosis	46 (32)
Smoking history	
Never	103 (71)
Former	32 (22)
Current	11 (8)
BMI, median (range), kg/m^2	27 (15-63)
BMI categories (WHO classification)	
Underweight: <18.5	5 (3)
Normal: 18.5-24.99	39 (27)
Overweight: 25-29.99	51 (35)
Obese: ≥ 30	50 (34)
Time from symptoms onset to presentation	
Median (range), d	2 (0-21)
Infection site at diagnosis	
URI	119 (82)
LRI	27 (18)
Laboratory abnormalities at presentation:	
Leukocytosis (WBC >11,000/mm)	8 (5)
Neutropenia (ANC <500 cells/mL)	10 (7)
Lymphocytopenia (ALC <200 cells/mL)	11 (8)
Elevated creatinine (>1.3 mg/dL)	23 (16)
Decreased albumin (<3.5 g/dL)	37 (25)
Hypoxia at diagnosis	10 (7)
Coinfections (within 1 month of diagnosis)	22 (15)
Respiratory copathogens	16 (11)
Outcomes	
Progression from URI to LRI	6/119 (5)
Overall LRI	33 (23)
Admission to the hospital	62 (42)
Length of stay	
Median (range), d	7 (1-74)
ICU admission	
On admission	3 (2)
Later	9 (6)
Mechanical ventilation	7 (5)
Oxygen supplement	22 (15)
Antiviral therapy	
Anytime during the episode	121 (83)
Within 48 hours of symptoms onset	26 (18)
Within 48 hours of diagnosis	38 (26)
Death within 30 days from date of diagnosis	
All-cause mortality	7 (5)
Influenza-related death	6 (4)

Data presented are n (%), unless otherwise indicated.
GVHD indicates graft-versus-host disease; WHO, World Health Organization; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; ICU, intensive care unit.

scoring index was not based on virus-specific factors, it may be extrapolated to other respiratory viruses, such as influenza, in HCT recipients.

In this study, we aimed to compare the clinical characteristics and outcomes of influenza infection, including the pandemic 2009/H1N1, strains from the subsequent seasons, and the current 2014/H3N2 influenza strain in HCT recipients, especially in view of the reported decreased efficacy of the 2014-2015 influenza vaccine (the main circulating virus during the past season was influenza A/2014/H3N2, which was a drifted strain that was not included in the current vaccine) [16]. We also applied the ISI to stratify HCT recipients according to their risk of severe influenza infection to compare their probabilities for serious complications such as LRI and death.

MATERIALS AND METHODS

We conducted a retrospective study and included all HCT recipients with laboratory-confirmed influenza infection from July 2009 to December 2013 at the University of Texas MD Anderson Cancer Center in Houston, Texas. The institutional review board approved the protocol and waived the requirement for obtaining informed consent.

We also examined the clinical characteristics and outcomes of patients with 2014/H3N2 influenza A infections from November 2014 to December 2014 and compared those with the 4 previous seasons. We collected the following data from medical chart review: demographic information including age, sex, race, body mass index (BMI), and smoking status; cancer type; type of HCT; time from HCT to influenza infection; type of conditioning regimen; use of myeloablative regimen within 100 days before the diagnosis of influenza infection; coinfections; use of immunosuppressive therapy within the month preceding the diagnosis of influenza A infection; and detailed information on clinical characteristics, laboratory test results, and radiologic characteristics upon presentation. Data about treatment and the outcomes, such as length of hospital stay, development of LRI, admission to intensive care unit, mechanical ventilation, oxygen supplementation, and death, were also recorded.

Definitions

An influenza case was defined as any HCT recipient who developed acute respiratory illness and had influenza confirmed via viral culture and/or a direct fluorescent antigen test. The polymerase chain reaction (PCR) assay was only available and used during the 2014/H3N2 influenza season. *Upper respiratory tract infection* (URI) was defined as the onset of any of the following symptoms: fever, cough, rhinorrhea, sore throat, earache, or nasal or sinus congestion with a normal or unchanged chest radiograph or chest computed tomography scan at the time of influenza virus infection confirmed via nasal wash. *LRI* was defined as the onset of any of the previous symptoms with chest imaging (chest radiograph or chest computed tomography scan) demonstrating new or worsening pulmonary infiltrates suggestive of viral infection at the time of influenza virus infection confirmed via any respiratory specimen, including nasal wash, sputum, bronchoalveolar washing or lavage, or endotracheal tube aspirate. A *nosocomial infection* was defined as the onset of respiratory symptoms at least 48 hours after admission. *Severe neutropenia* was defined as an absolute neutrophil count of < 500 cells/mL, and *severe lymphocytopenia* was defined as an absolute lymphocyte count of < 200 cells/mL. *All-cause mortality* was defined as death from any cause within 30 days of the diagnosis of influenza infection, and mortality was attributed to influenza if a persistent or progressive influenza infection with respiratory failure was present at the time of death. Antiviral therapy was considered to be early if it were started within 48 hours of diagnosis.

ISI

In a previous study [15], we developed an ISI in HCT recipients with RSV infection, using variables related to the host such as age, low neutrophil and lymphocyte counts, the nature of the conditioning regimen used, time from transplantation, the presence of complications such as graft-versus-host disease, and corticosteroid use (Supplemental Table). This scoring index