Biology of Blood and Marrow Transplantation 7:11S-13S (2001)

Community-Acquired Respiratory Syncytial Virus and Parainfluenza Virus Infections After Hematopoietic Stem Cell Transplantation: The Fred Hutchinson Cancer Research Center Experience

W. Garrett Nichols, Ted Gooley, Michael Boeckh

Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington

Correspondence and reprint requests: W. Garrett Nichols, MD, MSc, Research Associate, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, D3-100, Seattle, WA 98109 (e-mail: gnichols@fhcrc.org).

ABSTRACT

Community respiratory viruses (CRVs) are an important cause of morbidity and mortality among recipients of hematopoietic stem cell transplants (HSCT). At the Fred Hutchinson Cancer Research Center, respiratory syncytial virus (RSV) and parainfluenza virus (PIV) infections in HSCT recipients have been studied intensively for more than a decade. Over time, mortality from these infections has declined as the approach to diagnosis has become more aggressive and more stringent preventive measures have been instituted. However, mortality among HSCT recipients with RSV or PIV pneumonia remains high. Uncontrolled studies at our center suggest that prompt therapy with aerosolized ribavirin has reduced mortality from RSV pneumonia but does not appear to affect the course of established PIV pneumonia. Two controlled clinical trials of ribavirin therapy for RSV infection in HSCT recipients are in progress.

KEY WORDS

Hematopoietic stem cell transplant • Respiratory syncytial virus • Parainfluenza virus

INTRODUCTION

Community respiratory viruses (CRVs) include the influenza viruses, parainfluenza virus (PIV), respiratory syncytial virus (RSV), rhinoviruses, and adenoviruses. These viruses not only cause respiratory tract infections in the community but also are associated with pneumonia and increased mortality among recipients of hematopoietic stem cell transplants (HSCTs). The pattern of CRV infection among HSCT recipients mirrors that in the surrounding community, but these highly contagious infections also have a high potential for nosocomial spread [1-5].

At the Fred Hutchinson Cancer Research Center (FHCRC), we have studied CRV infections in the HSCT population since 1988. Epidemiologic data are collected through active surveillance. Nasopharyngeal wash and throat swab specimens are obtained from all HSCT recipients with symptoms of respiratory virus infections, and the specimens are tested for CRVs by the direct florescent antibody (DFA) test as well as by shell vial culture and conventional culture. The same tests are applied to all bronchoalveolar lavage (BAL) samples, sinus aspirates, lung biopsies, and autopsy specimens.

Retrospective analyses of risk factors for RSV [6] and PIV [7] infections in HSCT recipients at FHCRC have recently been completed and are summarized here, along with an overview of uncontrolled treatment trials and information on 2 ongoing trials of treatment for RSV infection.

RSV INFECTIONS

Epidemiology

The first CRV to be studied systematically at FHCRC was RSV, which is associated with serious morbidity and high mortality among HSCT recipients [8,9]. RSV infection is seasonal, with the majority of infections occurring between January and April and virtually no infections occurring between August and October. As shown in Figure 1, serious RSV pneumonia outbreaks occurred at FHCRC in 1990 (31 patients with RSV infection, 18 with RSV pneumonia), 1994 (28 patients with RSV infection, 12 with RSV pneumonia), and 1997 (41 patients with RSV infection, 24 with RSV pneumonia).

From 1989 to 1999, RSV infection developed in 171 of 3897 HSCT recipients. The overall attack rate was 4.5%,

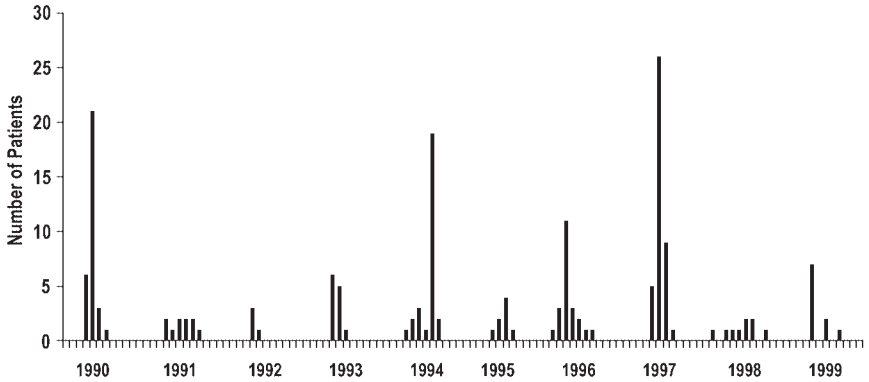

Figure 1. Respiratory syncytial virus pneumonia outbreaks among HSCT recipients at Fred Hutchinson Cancer Research Center, 1990 to 1999. Major outbreaks occurred in 1990, 1994, and 1997.

but the attack rate among patients who received transplants during the winter RSV season was approximately 10%. A total of 103 (60%) patients had upper respiratory tract infections (URTIs) alone, 54 (32%) had URTIs that progressed to pneumonia at a median of 7 days after the onset of upper respiratory tract symptoms, and 14 (8%) had pneumonia alone without preceding upper respiratory tract signs or symptoms. The occurrence of BAL-proven RSV pneumonia in the absence of signs attributable to a CRV highlights the importance of testing all BAL specimens for the presence of these viruses.

Risk Factors

At FHCRC, we recently completed a retrospective analysis of risk factors for RSV infection and progression to pneumonia in HSCT recipients from 1989 to 1999 [6]. Our goals were to identify risk factors for development of RSV URTI, to identify characteristics that predict progression of RSV URTI to RSV pneumonia, and to determine the impact of RSV infection on overall mortality among HSCT recipients. Surveillance for RSV infection was conducted as described above. RSV URTI was defined as detectable RSV in the nasopharynx, throat, or sinuses; RSV pneumonia was defined as radiographic and clinical evidence of pneumonia in the presence of RSV in BAL fluid and/or lung tissue specimens. Between 1994 and 1997, this retrospective analysis included some patients with RSV URTI who had participated in a pilot study of preemptive treatment with low-dose aerosolized ribavirin (2 g given once over 2 hours/d).

In a univariate analysis, male sex was found to increase the risk of contracting any RSV infection (Table 1). Age, donor type, use of total body irradiation (TBI), cytomegalovirus (CMV) serostatus, herpes simplex virus (HSV) serostatus, underlying disease, source of stem cells, engraftment status, presence of graft-versus-host disease (GVHD), and year of HSCT had no impact on RSV infection risk.

Because of the interest in preemptive treatment to prevent progression of RSV URTI to pneumonia, risk factors for disease progression were analyzed (Table 1). In a multivariate analysis, older age was significantly associated with progression to pneumonia, as was the receipt of stem cells from a mismatched or unrelated donor. Underlying disease, use of TBI, CMV serostatus, HSV serostatus, preemptive use of low-dose aerosolized ribavirin (2 g once a day), and acute GVHD did not significantly affect the risk of disease progression to pneumonia. The use of corticosteroids was not considered in this model.

Finally, the effect of RSV infection on mortality after HSCT was determined by multivariate analysis adjusted for age, sex, underlying disease and disease risk, donor type, use of TBI, CMV serostatus, HSV serostatus, source of stem cells, and year of transplant (Table 1). Any RSV infection acquired after HSCT was found to increase mortality risk by 60%.

PIV INFECTIONS

Epidemiology

We recently completed and published a comprehensive analysis of parainfluenza virus (PIV) infections after stem cell transplantation at our center [7]. Indeed, the most common CRV infection at FHCRC in the period between 1990 and 1999 was PIV. Except for outbreaks in 1993, 1998, and 1999, PIV occurred at a relatively constant rate. The variations in PIV incidence throughout the year were much less pronounced than those for RSV; June, July, and October were the months of peak PIV incidence.

From 1990 to 1999, 253 cases of PIV infection occurred among 3577 HSCT recipients, an attack rate of 7.1%. Of these cases, 228 (90%) were caused by PIV-3. The clinical presentation of PIV-3 differed from that of RSV: 87% of patients had signs and symptoms of URTI alone; 6% had

Table 1. *Risk Factors for RSV Infection, Progression to RSV Pneumonia, and Overall Mortality Among 3897 HSCT Recipients at FHCRC, 1990 to 1999**

Risk Factor	Hazard Ratio	95% CI	P
For RSV infection			
Male sex	1.4	1.04-2.0	.03
For progression to pneumonia			
Age (continuous)	—	—	.005
Mismatched/unrelated donor	2.8	1.4-5.7	.006
For impact on mortality			
Any RSV infection (time dependent)	1.6	1.3-2.0	<.001

*Data from [6]. CI indicates confidence interval.

Table 2. *Risk Factors for PIV Infection, Progression to Pneumonia, and Overall Mortality Among 3577 HSCT Recipients at FHCRC, 1991 to 1999**

Risk Factor	Hazard Ratio	95% CI	P
For PIV acquisition			
Unrelated donor	1.6	1.1-2.3	.02
For progression to pneumonia			
No corticosteroids	1.0		
<1 mg/kg per d of corticosteroids	2.5	0.7-8.3	.14
1 to <2 mg/kg per d of corticosteroids	6.4	2.1-19.0	.0009
≥2 mg/kg per d of corticosteroids	19.8	5.5-68.3	<.0001
For impact on mortality			
No PIV infection	1.0		
Any PIV infection	1.6	1.3-1.9	<.0001
PIV URTI	1.3	1.1-1.6	.02
PIV LRTI	3.4	2.4-4.7	<.0001

*Data from [7].

signs and symptoms of both URTI and lower respiratory tract infection (LRTI); and 7% had only LRTI signs and symptoms. Among those who presented with URTI alone, infections progressed to LRTI in 13%, at a median of 3 days. There were a total of 55 PIV-3 LRTIs.

Risk Factors

In a univariate analysis, the use of an unrelated stem cell donor was found to be the only factor significantly associated with an increased risk of PIV-3 infection (Table 2). Age, conditioning regimen, CMV serostatus, underlying disease, engraftment status, and presence of GVHD had no significant effect on the incidence of PIV infection.

In a multivariate analysis, the risk of progression of PIV-3 URTI to pneumonia was found to be increased by the use of corticosteroids, in a dose-dependent fashion (Table 2); patients receiving corticosteroids at a dosage of ≥2 mg/kg per day had a 19.8-fold increase in risk. Patient age, donor age, donor type, CMV serostatus, underlying disease, use of TBI, engraftment status, and presence of GVHD had no significant effect on progression to PIV pneumonia once corticosteroids were in the model.

The effect of PIV-3 infection on mortality after HSCT was also analyzed, in a multivariate analysis adjusted for age, CMV serostatus, donor type, and underlying disease (Table 2). Any PIV-3 infection was associated with a 1.6-fold increase in mortality risk; a greater increase in mortality risk was found for patients with PIV-3 LRTI, although patients with PIV-3 URTI also had a statistically significant increase in the risk for overall mortality.

A factor contributing to increased mortality among HSCT recipients with PIV-3 infection may have been the presence of co-pathogens, which were found in 29 of 55 cases of PIV-3 LRTI. Mortality rates were much higher among HSCT recipients with a PIV-3 infection and a co-pathogen than among those without a co-pathogen. The most common co-pathogen was *Aspergillus fumigatus* (found in 13 patients), which causes highly lethal infections. Of note, in a separate analysis of risk factors for postengraftment aspergillosis among HSCT recipients at our center, PIV infection was found to be an independent predictor of late aspergillosis.

TREATMENT OF RSV INFECTION

HSCT Recipients With RSV Pneumonia at FHCRC

The mortality rate for RSV pneumonia among HSCT recipients at FHCRC has declined since 1990. In each of the 3 RSV outbreaks in the past decade, some patients with RSV pneumonia were treated empirically with aerosolized ribavirin (1990 and 1997) or intravenous ribavirin (1994). In 1990, 13 of 18 patients with RSV pneumonia were treated with aerosolized ribavirin [8]. Most did not receive the full course of therapy, 6 g of aerosolized ribavirin over 18 hours in each 24-hour period for 10 days. The mortality rate was approximately 70% among treated patients; all survivors were treated for ≥5 days. Mortality was 100% among the 5 untreated patients.

Between November 1993 and May 1994, 10 patients with RSV pneumonia received intravenous ribavirin (loading dose, 35 mg/kg in 3 divided doses every 8 hours; maintenance dose, 25 mg/kg in 3 divided doses every 8 hours for 6 days) [10]. Two (20%) patients survived, both of whom had few radiographic infiltrates and required only minimal supplemental oxygen. In 2 patients, hemolysis developed that required premature discontinuation of therapy [10]. In 1997, we thus returned to the use of aerosolized ribavirin (2 g aerosolized ribavirin over 2 hours 3 times daily for 10 days) for 24 patients with BAL-confirmed RSV pneumonia. The mortality rate for this population was 33% (unpublished data).

Although a formal statistical analysis has not yet been completed, several factors may have contributed to the great difference in RSV mortality rates between those treated with aerosolized ribavirin during the 1990 RSV outbreak and those treated during the 1997 RSV outbreak. The most important of these factors was a decrease in the time to diagnosis. In 1990, diagnosis was generally delayed in patients with signs and symptoms of pneumonitis. Nasopharyngeal specimens were obtained after several days, and BAL fluid was often obtained only if URTI specimens were negative for RSV. By 1997, however, the approach to diagnosis was more aggressive, with BAL specimens being obtained and tested early in the course of illness. At the start of aerosolized ribavirin therapy, most patients in the 1990 cohort required high-dose supplemental oxygen or mechanical ventilation, whereas few patients in the 1997 cohort required any supplemental oxygen. This fact suggests that aerosolized ribavirin may be most effective when used early in the course of RSV pneumonia, which mandates rapid diagnostic algorithms.

Another factor that could have contributed to the widely different mortality rates was the addition of intravenous immunoglobulin (IVIG) to aerosolized ribavirin for 19 of 24 patients treated in 1997. In a univariate analysis, however, survival was similar among patients who received concomitant pooled IVIG and those who did not.

Ongoing Controlled Clinical Trials

In recent years, most transplantation centers have reported lower RSV mortality among HSCT recipients, but in the absence of data from controlled clinical trials, it has

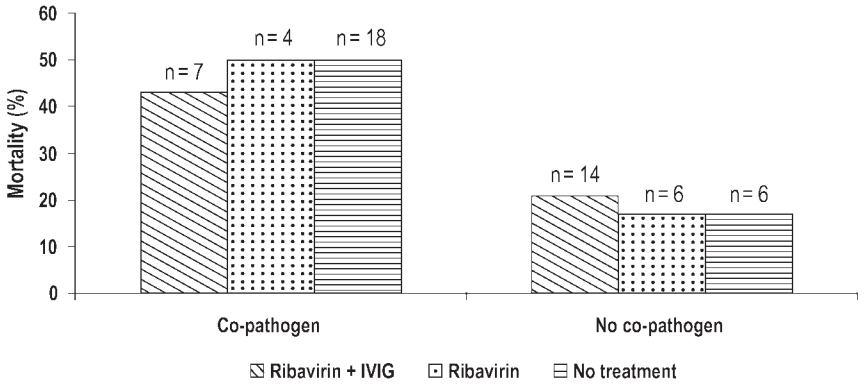

Figure 2. Thirty-day mortality rates for 55 HSCT recipients at Fred Hutchinson Cancer Research Center with PIV-3 LRTI with or without a co-pathogen after treatment with aerosolized ribavirin plus intravenous immunoglobulin (IVIG), treatment with aerosolized ribavirin, or no treatment. (From Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood*. 2001;98:573-578. Copyright American Society of Hematology, used by permission.)

been difficult to evaluate the benefits of treatment or to compare regimens. Two controlled clinical trials that may provide such data are currently in progress.

Aerosolized Ribavirin Plus Palivizumab. The efficacy of aerosolized ribavirin plus palivizumab (a monoclonal RSV antibody preparation) is currently being evaluated in a comparative randomized controlled clinical trial conducted by the Collaborative Antiviral Study Group (CASG) and the National Institute of Allergy and Infectious Diseases (NIAID). In this study, HSCT recipients with RSV LRTI are treated with aerosolized ribavirin with or without palivizumab. The primary end point is all-cause mortality at 28 days after randomization; secondary end points include days of hospitalization, days in the intensive care unit, days of mechanical ventilation, and safety outcomes.

Aerosolized Ribavirin to Prevent Progression to Pneumonia. Progression to pneumonia occurs in approximately 50% of HSCT recipients with RSV URTI [1,4,8]. Once established, RSV pneumonia leads to death in 45% to 80% of these patients.

The treatment of RSV URTI with aerosolized ribavirin has been examined in several pilot studies, including 1 at FHCRC (unpublished observations) and 1 at M.D. Anderson Cancer Center (MDACC) [7]. In the FHCRC study, as noted above, aerosolized ribavirin (2 g once daily for 5-7 days) had no effect on progression to pneumonia. In the MDACC study, 14 patients were treated with aerosolized ribavirin (6 g daily)—in either a conventional regimen (20 mg/mL 3 times daily over 18 hours/d) or a high-dose, short-duration regimen (60 mg/mL for 2 hours 3 times daily)—plus IVIG (500 mg/kg every other day) [7]. The URTI resolved in 10 (71%) patients; pneumonia developed in the other 4 patients (during preengraftment in 3), 2 of whom died [11]. However, comparison with historical controls and formal statistical analysis were not performed in this study.

The prevention of progression of RSV URTI to pneumonia in HSCT recipients is being addressed in a second ongoing multicenter CASG/NIAID study (CASG-202). In this phase III study, the safety and efficacy of aerosolized ribavirin are being evaluated in HSCT recipients with RSV URTI infection and without signs of LRTI. The study patients are randomized to treatment with aerosolized ribavirin (2 g 3 times daily for 10 days) or to placebo and close daily observation. The primary end point of the study is progression to pneumonia, which is assessed by an evaluator blinded to the patients' treatment assignments. Secondary end points are RSV pneumonia, confirmed by the results of culture or a DFA test, and safety evaluations.

To be eligible for study entry, HSCT patients must have signs and symptoms of URTI and RSV infection confirmed by DFA or shell vial tests of nasopharyngeal wash specimens. Patients must have undergone HSCT ≤90 days previously, or ≤180 days previously if the stem cell donor was unrelated or if stem cells came from cord blood. HSCT recipients who underwent transplant from other sources ≥90 days previously but who have GVHD requiring systemic corticosteroids in a daily dose of >1 mg/kg are also eligible.

To detect a reduction in risk of progression to pneumonia from 50% (background) to 20% with 80% power at the 5% significance level, a sample size of 90 patients is required. Patients are stratified by engraftment status and transplant type (mismatched and unrelated donors versus other types).

TREATMENT OF PIV INFECTION

PIV-3 infections are relatively common among HSCT recipients and are an independent risk factor for increased mortality. PIV infections appear to be less responsive to aerosolized ribavirin than RSV infections. Once PIV-3 pneumonia was established, the use of ribavirin with or without IVIG at our center had no effect on 30-day mortality rates, even after stratification for co-pathogens (Figure 2) [7]. Overall mortality was lower among patients with PIV-3 LRTI who had no co-pathogen. Because progression to pneumonia is common among those with ongoing treatment with corticosteroids, one should consider decreasing immunosuppression if at all possible for those with PIV URTIs.

PREVENTION OF CRV INFECTIONS

In the absence of treatments with proven efficacy against CRV infections in HSCT recipients, prevention of

such infections is the first line of defense. Strict enforcement of hand washing is the mainstay of protection, while the use of masks to prevent droplet transmission is more controversial. Standard infection-control procedures at FHCRC have included strict respiratory isolation for patients with symptoms of URTI until cultures are negative for CRVs, but this policy alone did not prevent the 1997 RSV outbreak. Subsequent investigation of this outbreak indicated that a single infected healthcare worker was probably the source of infection of 10 patients within a 10-day period. We therefore instituted a sign-in policy during winter respiratory virus seasons. Before entering the transplantation ward, staff and visitors must state that they are free of all URTI symptoms. Staff members with any symptoms must remain absent from work until the symptoms have resolved. Because the cost of staffing during the winter RSV season is high, this policy requires a major institutional commitment.

This policy may have reduced the incidence of RSV infection, but the largest outbreak of PIV-3 infection occurred in 1999, after the policy had been in effect for several years. The incidence of PIV-3 infection does not have great seasonal variations, so the winter sign-in policy did not affect the incidence of infections during the spring and summer. However, the PIV-3 outbreaks in 1998 and 1999 occurred during the winter season, when the sign-in policy was in effect, and without a great increase in PIV infections in the surrounding community. The outbreak continued over a 6-month period, and the incidence of PIV-3 was similar in inpatient and outpatient units. Contrary to expectations, 10 of 19 isolates obtained from patients at different locations and at different times had identical sequences (unpublished data). These findings suggest that PIV infections in immunocompetent persons (such as healthcare workers) may result in viral shedding, even while the host is asymptomatic. Prevention of PIV infections, even with the use of strict infection-control strategies, may be difficult.

CONCLUSIONS

CRV infections remain significant causes of morbidity and mortality among HSCT recipients. Both RSV and PIV infections may progress from URTI to pneumonia, and mortality due to pneumonia is high. Current treatment options for PIV infections are limited, while those for RSV are more promising. Ongoing clinical trials should provide new data on optimal therapy for RSV infection and prevention of the progression of RSV URTI to pneumonia. Vaccines for RSV and PIV that could be used among healthcare workers and caregivers are badly needed to limit nosocomial spread of these viruses, as are new medications that are active against PIV. For now, infection control must be accorded high priority in the care of the immunocompromised HSCT recipient.

REFERENCES

1. Bowden RA. Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. *Am J Med*. 1997;102(3A):27-30.
2. Englund JA, Anderson LJ, Rhame FS. Nosocomial transmission of respiratory syncytial virus in immunocompromised adults. *J Clin Microbiol*. 1991;29:115-119.
3. Elting LS, Whimbey E, Lo W, Couch R, Andreeff M, Bodey GP. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. *Support Care Cancer*. 1995;3:198-202.
4. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med*. 1997;102(3A):2-9.
5. Garcia R, Raad I, Abi-Said D, et al. Nosocomial respiratory syncytial virus infections: prevention and control in bone marrow transplant patients. *Infect Control Hosp Epidemiol*. 1997;18:412-416.
6. Boeckh M, Gooley T, Bowden RA, et al. Risk factors for progression from respiratory syncytial virus upper respiratory tract infection to pneumonia after hematopoietic stem cell transplantation. Presented at the 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999; San Francisco, Calif.
7. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood*. 2001;98:573-578.
8. Harrington RD, Hooton TM, Hackman RC, et al. An outbreak of respiratory syncytial virus in a bone marrow transplant center. *J Infect Dis*. 1992;165:987-993.
9. Whimbey E, Couch RB, Englund JA, et al. Respiratory syncytial virus pneumonia in hospitalized adult patients with leukemia. *Clin Infect Dis*. 1995;21:376-379.
10. Lewinsohn DM, Bowden RA, Mattson D, Crawford SW. Phase I study of intravenous ribavirin treatment of respiratory syncytial virus pneumonia after marrow transplantation. *Antimicrob Agent Chemother*. 1996;40:2555-2557.
11. Ghosh S, Champlin R, Englund J, et al. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant*. 2000;25:751-755.