



Community Respiratory Virus Infections in Bone Marrow Transplant Recipients: The M.D. Anderson Cancer Center Experience

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ABSTRACT

Community respiratory virus (CRV) infections are common among bone marrow transplant (BMT) recipients during community outbreaks. At M.D. Anderson Cancer Center (MDACC), experience with CRV infection in this population over the past decade suggests that BMT recipients in the preengraftment phase are at special risk of progression of upper respiratory tract infection (URTI) to pneumonia. After pneumonia is established, no currently available therapy substantially reduces mortality. For BMT recipients with respiratory syncytial virus URTIs, treatment with ribavirin and intravenous immunoglobulin may be helpful in preventing progression to pneumonia and thus in reducing mortality, but this approach requires confirmation in controlled clinical trials. Prevention of CRV infection in this vulnerable patient population is crucial to reducing morbidity and mortality. Aggressive infection control precautions, which have been in effect at MDACC since 1994, have reduced nosocomial transmission of these potentially lethal infections.

KEY WORDS

Respiratory syncytial virus • Bone marrow transplant • Pneumonia

INTRODUCTION

During the past decade, our understanding of community respiratory virus (CRV) infections in immunocompromised adults, including bone marrow transplant (BMT) recipients and patients undergoing intensive therapy for leukemia, has greatly expanded. Prior to the early 1990s, the impact of CRV-related complications in this population was largely underestimated. In 2001, as the result of studies at M.D. Anderson Cancer Center (MDACC) and elsewhere, it is understood that CRV infections, which rarely cause complications in healthy adults, can cause substantial morbidity and mortality among immunocompromised adults. As our understanding has grown, our approach to diagnosis and management of these infections has changed substantially. The results of a decade of studies of CRV infection in immunocompromised adults at MDACC are summarized here.

EPIDEMIOLOGY OF CRV INFECTION IN IMMUNOCOMPROMISED ADULTS

There are notable center-to-center differences in the incidence of CRV infections in immunocompromised adult

patients. These differences depend, in part, on the infection rates in the surrounding communities, but they are also influenced by the rigor with which diagnosis is pursued and by the intensity of immunosuppressive treatment prior to infection onset, which may affect the morbidity and mortality associated with the infection. At MDACC, during the winter influenza season, CRV infections are the cause of approximately 20% to 30% of the hospitalizations required for adult patients undergoing treatment for leukemia and adult BMT recipients.

In a surveillance study conducted at MDACC during the 1992-to-1993 and 1993-to-1994 winter influenza seasons, for example, culture-confirmed CRV infections occurred in 21% of all adult BMT recipients, caused pneumonia in 12%, and were responsible for death in 6%. Allogeneic BMT recipients had a higher risk of infection than did autologous BMT recipients (29% versus 16%). However, mortality—unlike that reported in the European Group for Blood and Marrow Transplantation study (*see* Ljungman, this supplement)—was similar in allogeneic and autologous BMT recipients (7% and 6%, respectively), because many autologous BMT recipients at MDACC also received intensive therapy for leukemia or lymphoma.

Table 1. Factors Influencing Mortality in RSV Pneumonia in 23 Adult BMT Recipients at MDACC

Factor	Early Treatment, Died/Treated, n (%)	Late or No Treatment, Died/Treated, n (%)
Autologous BMT (n = 12)	3/7 (43)	5/5 (100)
Allogeneic BMT (n = 11)	2/7 (29)	4/4 (100)
Preengraftment (n = 8)	2/5 (40)	3/3 (100)
Postengraftment (n = 15)	3/9 (33)	6/6 (100)

During these 2 winter influenza seasons, CRV infections became the leading cause of viral pneumonia and viral pneumonia mortality in hospitalized BMT recipients with an acute respiratory illness, whereas CMV-related pneumonia and pneumonia mortality diminished in importance. Of the 48 viral pneumonia cases, 39 were attributed to CRVs and 9 to CMV; 25 deaths occurred, with 20 being attributed to CRV infections and 5 to CMV infections. Among adult BMT recipients at MDACC today, CRV infection is a major cause of death, second only to *Aspergillus* infection.

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

Incidence and Mortality

In studies of respiratory syncytial virus (RSV) infections in adult BMT recipients, the time at which RSV infection occurs has been shown to be a major influence on the clinical presentation as well as the outcome. In BMT recipients with RSV infections that occur before engraftment, RSV infection typically progresses from an upper respiratory tract infection (URTI) to a lower respiratory tract infection (LRTI), including pneumonia. Progression from a URTI to pneumonia is much less frequent in BMT recipients after engraftment. Among 46 patients at MDACC with RSV URTIs, pneumonia developed in 16 (80%) of 20 patients infected before engraftment but in only 7 (27%) of 26 patients after engraftment. Mortality rates among patients with RSV pneumonia were high no matter when infection occurred; pneumonia-related death occurred in 10 (63%) of 16 and 4 (57%) of 7 patients in the preengraftment and postengraftment groups, respectively.

Death of BMT recipients with RSV infection is usually related to the infection. Postmortem examinations generally reveal RSV to be the dominant pathogen in the lungs of these patients; only rarely are bacterial superinfections also present.

Early Versus Late Treatment

In evaluating the efficacy of treatment of RSV infection in BMT recipients, both the time after BMT and the time at which treatment was initiated should be considered. Because the risk of pneumonia is greater among preengraftment than postengraftment patients and mortality is high once pneumonia develops, treatment should have the greatest benefit when initiated early in preengraftment BMT recipients with RSV URTIs.

The effect of BMT stage (preengraftment versus postengraftment) and time of treatment initiation on mortality due to RSV pneumonia in 23 adult BMT recipients at

MDACC are shown in Table 1. Early treatment was associated with 40% mortality among the preengraftment patients and 33% mortality among the postengraftment patients. In contrast, late or no treatment resulted in 100% mortality in both groups. Early and late treatment had similar effects on mortality in autologous and allogeneic BMT recipients.

Available Therapies

Aerosolized ribavirin has been approved in the United States for the treatment of serious RSV LRTIs in young children. There are no efficacy data from controlled clinical trials in immunocompromised adults, although 1 such trial is currently enrolling patients (*see* Nichols, this supplement). Conflicting results have been reported in several small open trials, with the best results being obtained when therapy is initiated early [1-4]. Similarly, monotherapy with intravenous immunoglobulin (IVIG) may modify RSV infections. RSV-IVIG or monoclonal RSV antibody has been evaluated in children with RSV, but few studies have evaluated its use in treating adults [4].

Aerosolized Ribavirin Plus Intravenous Immunoglobulin

Many recent open treatment trials in immunocompromised adults have used combination therapy with aerosolized ribavirin and an IVIG preparation [4,5]. Since 1992, we at MDACC have treated adult BMT recipients who have RSV pneumonia with aerosolized ribavirin (6 g daily) in combination with 1 of several immunoglobulin preparations (standard IVIG, "hot lots" of IVIG containing high concentrations of RSV-neutralizing antibodies, monoclonal RSV antibodies, and RSV-IVIG) [4-6]. Our experience to date is summarized in Table 2. When therapy was initiated early, the mortality rate was 28%, compared with 60% to 100% when patients were not treated, were treated late, or were intolerant of ribavirin.

MDACC APPROACH TO TREATMENT OF RSV INFECTION

Time of Infection

The current approach to treatment of RSV infection in BMT recipients at MDACC depends on when the infection occurs following transplantation. If RSV URTI occurs within 1 month of transplantation, aerosolized ribavirin and

Table 2. Mortality Associated With RSV Pneumonia in Adult BMT Recipients Treated With Aerosolized Ribavirin and IVIG: MDACC, Winters, 1992-1993 to 1999-2000

Time of Therapy	No. of Patients With Pneumonia	Associated Mortality, %
All	66	44
Early (all immunoglobulins)	46	28
Standard IVIG	27	22
"Hot lots"	13	31
Monoclonal RSV antibody	3	33
RSV-IVIG	3	67
Late	9	100
None	10	60
Ribavirin intolerance	1	100

IVIg are initiated promptly to prevent progression to pneumonia. If RSV infection occurs more than 1 month after transplantation, the decision about appropriate therapy is based on clinical judgment. The patient's overall condition, concurrent therapy, and many other factors must be considered. If the RSV infection appears to be progressing, treatment should be initiated. If the patient is stable, he or she may be closely monitored without treatment.

Infection Control Strategy

The most important factor in limiting RSV mortality in BMT recipients is the recognition that infections caused by CRVs, including RSV, are common and contagious. At MDACC, patients are rigorously screened for CRV infections before transplantation. If symptoms are present, even if culture and rapid detection tests are negative for RSV, transplantation is delayed until the symptoms have resolved. Education about CRV infections is offered to patients, their families, and staff members. Patients are encouraged to wash their hands frequently and to take other precautions to avoid contamination with respiratory secretions. Only immediate family members are allowed to visit the patient, and they are urged to take the same precautions. Staff and visitors wear masks and gloves when entering patients' rooms. Staff members with respiratory infections are instructed to avoid patient contact while they are symptomatic. The time patients spend in crowded areas with a high potential for infection exposure should be limited; patients wear masks and gloves when they are in high-risk areas. Finally, rigorous efforts are made to identify, isolate, and treat BMT patients with respiratory infections. Since infection control procedures were initiated at MDACC, the incidence of nosocomial RSV infections among BMT recipients has declined dramatically [7].

CONCLUSIONS

CRV infections are common among BMT recipients during outbreaks of infection in the community. BMT

recipients in the preengraftment phase are at high risk for progression of URTI to LRTI. RSV pneumonia may be lethal at any time after BMT. Treatment with ribavirin and immunoglobulin early in the course of an RSV infection (before progression to pneumonia) appears to reduce mortality, but the efficacy of this regimen has not been confirmed in a controlled clinical trial. Because no available therapy has a reliable impact on mortality due to CRV pneumonia, prevention of infection is crucial. Aggressive infection control precautions can reduce nosocomial transmission of CRV infections.

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