Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia

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ABSTRACT

Background and Objectives

Little is known about respiratory syncytial virus (RSV) infection in patients with leukemia. The aim of this study was to determine the characteristics, and the outcome of RSV infection with or without therapy with aerosolized ribavirin in leukemia patients.

Design and Methods

We reviewed the records of 52 leukemia patients with RSV infection seen at our institution between October 2000 and March 2005.

Results

The median age of the patients was 47 years (range, 1-83 years). Most patients were male (65%) and had acute leukemia (65%); 46% had received salvage chemotherapy and 62% corticosteroids before RSV infection. Compared to the 25 patients with upper respiratory tract infection (URI), the 27 patients with pneumonia had a higher median APACHE II score at the time of the first assessment at the hospital for respiratory symptoms (11 vs 16), and a higher rate of corticosteroid treatment in the month preceding the infection (48% vs 74%) (all $p \leq 0.05$). Twenty-four (46%) patients received aerosolized ribavirin. Patients who presented with URI and were treated with ribavirin were less likely than non-treated patients to develop pneumonia (68% vs 96%, $p<0.01$) and possibly die of pneumonia (6% vs 36%, $p=0.1$). Multiple logistic regression analysis identified high APACHE II score and lack of ribavirin treatment as independent predictors of progression to pneumonia ($p=0.01$). Five patients (10%) died within 30 days of RSV infection; all had pneumonia.

Interpretation and Conclusions

RSV infection is associated with significant morbidity and mortality in leukemia patients; treatment with aerosolized ribavirin at the stage of URI may prevent pneumonia in some subsets of patients.

Key words: respiratory syncytial virus, leukemia, aerosolized ribavirin, pneumonia.

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Respiratory syncytial virus (RSV) is one of the most common respiratory viruses in cancer patients.[1-4] The reported incidence of RSV infection in adult hematopoietic stem cell transplant (HSCT) recipients and in patients with hematologic malignancies varies from 5% to 10%.[3, 5-7] RSV infection may present as upper respiratory tract infections (URI), such as pharyngitis or laryngitis, or a potentially fatal lower respiratory tract infections, such as tracheobronchitis, bronchiolitis, or pneumonia.[1-3] Up to 80% of RSV-associated URI in HSCT recipients and patients with hematologic malignancies may progress to lower respiratory tract infections, and the risk of progression is particularly great among severely myelosuppressed patients with lymphocytopenia.[1,3,5,8]

Previous reports of RSV pneumonia in HSCT recipients have described mortality rates ranging from 5% to 100%,[5,6,9-11] with conflicting reports on the use of antiviral therapy against this infection.[1,2,12-15] Recently, the first study in HSCT recipients that evaluated in a randomized, controlled fashion the role and safety of preemptive aerosolized ribavirin for preventing the progression of RSV URIs to pneumonia was terminated prematurely because of slow patient accrual over 5 years at three clinical sites,[16] reflecting the difficulty to carry such studies through to completion.

There is a paucity of literature about RSV infection in patients with leukemia who are not HSCT recipients (hereafter referred to as simply *leukemia patients*).[8, 17-19] The few studies reported to date suggest that the epidemiology, clinical course, and response to therapy for RSV infection in leukemia patients mirror the findings in HSCT recipients.[8,17] In leukemia patients, RSV seems to be a frequent cause of life-threatening infection, particularly among elderly patients, and to be associated with persistent myelosuppression, comorbidities, high APACHE II score, and pneumonia.[8,17] However, treating all leukemia patients with RSV infection is not reasonable, given the cost, safety profile and discomfort of ribavirin administration. To determine the characteristics and outcome of RSV infection in leukemia patients, we reviewed the records of all leukemia patients with such an infection seen at our institution between October 2000 and March 2005.

Design and Methods

Study design

Cases of RSV infection were identified by searching the microbiology laboratory and the infection control databases at the University of Texas, M.D. Anderson Cancer Center for patients evaluated between October 2000 and March 2005. The institutional review board approved the study, informed consent was waived, and patients' confidentiality was protected. The following information was abstracted from the patients' records: demographics details; the underlying leukemia; other conditions predisposing to infection, such as diabetes mellitus and chronic pulmonary disease; treatment with corticosteroids, chemotherapy, and radiotherapy; concomitant infections; and prior infections occurring within 4 weeks before the onset of RSV infection.

Specimen collection and laboratory procedures

Respiratory specimens (e.g., nasal wash specimens, bronchoalveolar lavage fluid) were collected from patients presenting with symptoms of respiratory infection. Respiratory specimens collected were examined at our microbiology laboratory. In brief, respiratory samples (5-10 mL) were collected in normal saline and placed in 5 mL of M4 transport medium (Remal, Lenexa, KS, USA). Each 5 mL specimen was adjusted to contain 0.5% bovine albumin, 100 μg of gentamicin, 1,000 IU of penicillin, 1,000 μg of streptomycin, and 2.5 μg of amphotericin B per mL final concentration (Gibco/Invitrogen, Carlsbad, CA, USA) and kept at 2°C to 6°C for 1 hour. Samples (0.2 mL each) were then inoculated into two tubes each containing the following tissue culture cell lines: human foreskin fibroblasts, Hep-2 larynx carcinoma, primary rhesus monkey kidney, and A549 human lung carcinoma. In addition, mink-lung/A549 mixed shell vials, African green monkey kidney/human embryonic lung fibroblast mixed shell vials, or MRC5 vials (Diagnostic Hybrids, Inc., Athens, OH, USA) were inoculated with 0.2 mL each of the specimen after this latter had been warmed at 35-C in a non-CO_2 incubator for 2 to 4 hours. This was followed by a centrifugation step lasting up to 1 hour. The first reading of the shell vials was made between 15 and 24 hours, and the final reading was done at 48 hours. The shell vials were discarded if they were negative at 48 hours. All tubes and vials were read and developed at appropriate times and confirmed using immunofluorescent staining. Hemadsorption studies were performed on days 2, 5, and 7. Both pooled and individual reagents were used containing monoclonal antibodies to RSV, adenovirus, rhinovirus, influenza A, influenza B, and parainfluenzae 1-4 (Light Diagnostics 3105 and 3108, Chemicon International, Temecula, CA, USA). Direct fluorescent antibody tests were performed to detect RSV and influenza antigens in samples (Light Diagnostics/ Simulfluor RSV/FluA 3129, Chemicon International).[1] Sixty-one percent of the direct samples were also cultured.

Definitions

RSV-associated URI was defined as rhinorrhea, nasal or sinus congestion, or cough without hypoxemia or infiltrates on chest radiography or chest computed tomography in a patient with RSV isolated in a specimen from the upper respiratory tract (e.g., nasal wash specimen, throat swab). RSV-associated pneumonia was defined as a clinical and radiographic presentation

compatible with viral pneumonia in a patient with RSV recovered from a bronchoalveolar lavage fluid, sputum, or tracheal aspirate sample. Chest radiography and chest computed tomography were performed in 96% of patients who tested positive for RSV and in all patients with clinical signs and symptoms suggestive of pneumonia. Neutropenia was defined as <500 neutrophils/mm^3 and lymphocytopenia as <1,000 lymphocytes/mm^3.

Therapy and outcome

Antiviral therapy was instituted at the discretion of the treating physician. Aerosolized ribavirin was administered at a daily dose of 6g and delivered at a concentration of 20 mg/mL for 18 hours per day by a small-particle aerosol generator unit (SPAG-2) via a face mask inside a scavenging tent to prevent environmental contamination. A split, intermittent dosing schedule was also used in some patients with RSV infection. With intermittent dosing, the daily dose of ribavirin was the same as that with the continuous schedule (6 g/day), but the concentration was 60 mg/mL given over 2 to 3 hours every 8 hours. Ribavirin was given either alone or combined with intravenous immunoglobulin (IVIG) or palivizumab. IVIG was administered at a dose of 500 mg/kg every other day for the duration of the ribavirin therapy. Palivizumab was administered as a single intravenous infusion of 15 mg/kg.

It is generally accepted that the first step in RSV replication is attachment of the viral particle to the nasal epithelium, and then the infection progresses down into the lower respiratory tract and causes pneumonia, particularly in immunocompromised patients.[20] Based on that, patients in our series who were initially seen with RSV pneumonia were considered to have had an URI before seeking medical attention. Response to ribavirin therapy was defined as complete resolution of clinical and radiologic manifestations of RSV infection. Response to therapy was assessed if ribavirin was administered for at least 48 hours. Patients were followed until resolution of all signs and symptoms of infection or death. Fatal outcome was assessed at 30 days after the diagnosis of RSV infection. RSV was considered a contributory cause of death if there was evidence of persistent or progressive RSV infection at the time of death. Co-infections in patients with RSV infection were considered potential contributory causes of death.

Statistical methods

The two primary end-points of the study were: (i) progression to pneumonia, (ii) mortality at 30 days of RSV infection. The significance of all the predictors for these outcomes was assessed in univariate analysis using Fisher's exact test or the χ^2 test, when appropriate. All variables with $p \leq 0.1$ on univariate analysis, and/or considered clinically relevant were included in multivariate logistic regression models. Odds ratios and 95% confidence intervals were calculated. Survival analysis on progression to pneumonia was performed for the patients who presented to our center with RSV URI. The patients were followed up for 30 days from the onset of the URI. The overall survival probability of progression to pneumonia was estimated by the Kaplan-Meier approach for the patients who were treated with ribavirin and those not treated with ribavirin, respectively, and were compared by a log-rank test. All data was analyzed using statistical analysis system (SAS) version 9.1 (SAS Institute Inc., Cary, NC, USA). Two-tailed p values of < 0.05 were considered statistically significant for this analysis.

Table 1. Characteristics of patients with leukemia and RSV infection (n = 52).

Characteristic	*No. of patients (%)*
Acute leukemia	34 (65)
Myeloid	18 (35)
Lymphoid	14 (27)
Other	2 (4)
Relapse of leukemia	24 (46)
Type of infection	
Upper respiratory	25 (48)
Pneumonia [a]	27 (52)
Median APACHE II score (range) [b]	15 (6-23)
Admission to intensive care unit	7 (13)
Neutropenia [c]	26 (51)
Lymphocytopenia [c]	43 (84)
Comorbidities	17 (33)
Co-infections [d]	9 (17)
Antiviral treatment [e]	24 (46)
Ribavirin monotherapy	10/24 (42)
Ribavirin plus intravenous immunoglobulin	10/24 (42)
Ribavirin plus palivizumab	4/24 (17)
Overall mortality	19 (37)
Days after RSV infection (range)	51 (3-415)
Death within 30 days after RSV infection	5 (10)

[a] *Including 13 patients in whom upper respiratory tract infection progressed to pneumonia.* [b] *At the time of the first assessment at the hospital for respiratory symptoms.* [c] *Information available for only 51 patients.* [d] *Within 1 month of the onset of RSV infection.* [e] *Administered for at least 48 hours.*

Results

Fifty-two patients with leukemia and RSV infection were identified. The incidence of RSV infection in leukemia patients increased during the study period. This finding was likely secondary to the increased number of patients tested for RSV infection during that period. The median age of the patients was 47 years (range, 1-83 years). Most of them (n=34; 65%) were male. The patients' clinical characteristics are listed in Table 1. Thirty-four patients (65%) had acute leukemia. Forty-five patients (87%) were admitted to our hospital. The seven non-admitted patients were

Table 2. Risk factors for progression to pneumonia in leukemia patients with RSV infection (n=52).

Characteristic	No. (%) of patients with pneumonia (n=27)	No. (%) of patients to pneumonia with URI without progression (n = 25)	*p* value (Fisher's exact test)	*p* value (multivariate analysis)
Gender, male/female	20/7	14/11	0.1	0.08
Leukemia in complete or partial remission	9 (33)	13 (52)	0.1	0.2
Median APACHE II score (range) [a]	16 (9-23)	11 (6-19)	0.002	0.01
Lymphocyte recovery (≥ 1,000/mm^3)	9/21 (43)	15/22 (68)	0.09	0.5
Comorbidities	12 (44)	6 (24)	0.1	0.1
Corticosteroids[b]	20 (74)	12 (48)	0.05	0.1
Prior use of cytarabine[b]	12 (44)	6 (24)	0.1	0.1
Antiviral treatment at URI state[c]				
Yes	1 (4)	8 (32)	0.009	0.009
No	26 (96)	17 (68)		
Overall mortality	11 (41)	8 (32)	0.5	
Days after RSV infection (range)	15 (3-94)	207 (51-415)	0.0007	
Death within 30 days after RSV infection	5/27 (19)	0/25 (0)	0.05	

[a]At the time of the first assessment for respiratory symptoms. [b] Within 1 month of the onset of RSV infection. [c] Ribavirin either alone or combined with intravenous immunoglobulin or palivizumab.

mildly symptomatic (six patients) or admitted to another center (one patient). None of them received RSV-directed therapy.

Twenty-four patients (46%) had received salvage chemotherapy and 32 (62%) were receiving corticosteroids before the onset of RSV infection. The most common presenting symptoms were cough (45 patients; 87%), fever (44 patients; 85%), runny nose (32 patients; 62%), and nasal/sinus congestion (30 patients; 58%). Fourteen patients (27%) had gastrointestinal complaints (e.g., nausea, vomiting, and diarrhea) at presentation. Co-infections at the time of the diagnosis of RSV infection were noted in nine patients (17%), five of these co-infections involved the lungs. Other respiratory viruses at the onset of the RSV infection were identified in two patients (both had a rhinovirus infection). Additionally, two more patients developed infection with other respiratory viruses within 30 days after the onset of the RSV infection (influenza A and adenovirus, in one patient each). Twenty-seven patients (52%) had pneumonia, and 25 (48%) had URI (Table 1). Compared to the patients with URI, patients with pneumonia had a longer median duration of symptoms (9 vs 20 days), a longer median hospital stay (6 vs 12 days), a higher rate of intensive care (0% vs 26%), a higher median APACHE II score at the time of the first assessment at the hospital for respiratory symptoms (11 vs 16), a higher rate of corticosteroid treatment within the month preceding the RSV infection (48% *vs.* 74%), and a lower rate of ribavirin therapy during the early stage of infection (96% *vs.* 68%) (all $p \leq 0.05$). There was a trend toward lymphocyte recovery being less common in patients with pneumonia than in those with URI (9 of 21 or 43% vs 15 of 22 or 68%, p=0.09) (Table 2). Thirteen (48%) of the 27 patients with pneumonia presented to our center with URI and subsequently developed pneumonia as inpatients. Two (15%) of these 13 patients had received corticosteroid therapy prior to the onset of pneumonia, compared with five (20%) of the 25 patients who presented with URI and did not develop pneumonia (p= 1.0).

One of the nine patients in whom ribavirin therapy was administered at the URI stage of infection experienced progression to pneumonia, whereas 26 of the 43 patients who received no therapy or in whom therapy was not initiated during the URI stage of infection developed pneumonia (p=0.009, Table 2). On multiple logistic regression analysis, high APACHE II score and lack of ribavirin therapy were independent predictors of progression to pneumonia (p≤0.01) (Table 2). In addition, there was a trend toward a higher rate of progression to pneumonia in males (74% vs 56%, p=0.08).

Twenty-four patients (46%) were treated with a ribavirin-based regimen, and five (10%) were treated with intravenous immunoglobulin alone. No patient received palivizumab alone. Twenty-three patients (44%) received no treatment (Table 3). The median duration of the ribavirin-based therapy was 7 days (range, 2 to 14 days), and the majority of patients (92%) received at least 4 days of such regimen. The rate of use of ribavirin-based therapy was relatively stable throughout the study period. The use of a ribavirin-based regimen seems to improve the outcome of patients with RSV pneumonia: one of 16 patients with RSV pneumonia who were treated with ribavirin died (at 30 days), compared with four of 11 patients with RSV pneumonia who were not treated with ribavirin (p=0.1) (Figure 1). In this subset of

Table 3. Characteristics of leukemia patients with RSV infection according to the use of antiviral therapy.

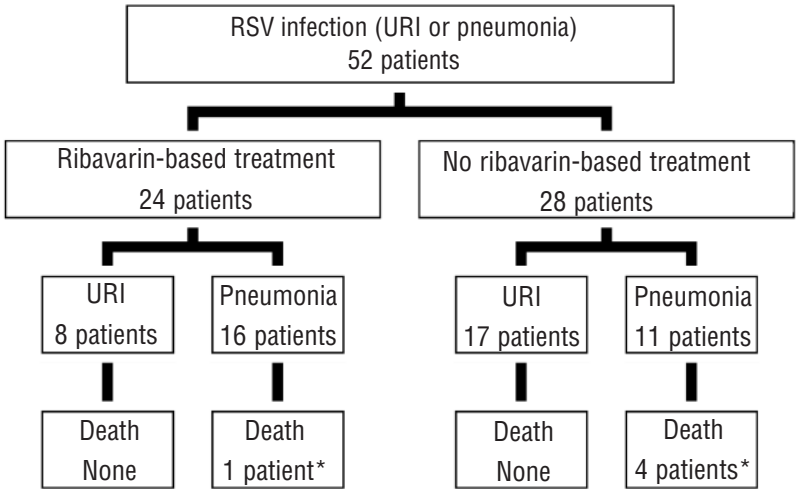
Characteristic	*No. (%) of patients treated with ribavirin alone (n= 10)*	*No. (%) of patients treated with ribavirin plus IVIG (n= 10)*	*No. (%) of patients treated with ribavirin plus palivizumab (n=4)*	*No. (%) of patients treated with IVIG alone (n=5)*	*No. (%) of patients who did not receive treatment (n=23)*
Median age (range)	53 (33-62)	55 (22-62)	56 (37-71)	52 (21-69)	56 (1-83)
Gender, male/female	6/4	9/1	3/1	2/3	14/9
Acute leukemia	10/10 (100)	7/10 (70)	0/4 (0)	1/5 (20)	16/23 (70)
Leukemia in complete or partial remission	5/10 (50)	3/10 (30)	1/4 (25)	1/5 (20)	12/23 (52)
Median APACHE II score (range)[a]	13 (9-17)	16 (6-23)	16 (12-17)	16 (10-17)	14 (6-20)
Neutropenia[b]	7/9 (78)	6/10 (60)	1/4 (25)	0/5 (0)	12/23 (52)
Lymphocytopenia[b]	8/9 (89)	9/10 (90)	3/4 (75)	4/5 (80)	19/23 (83)
Comorbidities	3/10 (30)	4/10 (40)	1/4 (25)	4/5 (80)	6/23 (26)
Corticosteroids[b]	9/10 (90)	6/10 (60)	2/4 (50)	1/5 (20)	14/23 (61)
Type of infection					
Upper respiratory tract	4/10 (40)	6/10 (60)	3/10 (30)	7/10 (70)	1/4 (25)
Pneumonia	3/4 (75)	2/5 (40)	3/5 (60)	15/23 (65)	8/23 (35)
Treatment at URI state	5/10 (50)	3/10 (30)	1/4 (25)	3/5 (60)	NA
Progression to pneumonia on therapy	1/10 (10)	0/10 (0)	0/4 (0)	1/4 (25)	NA
Death within 30 days after RSV infection	0/10 (0)	1/10 (10)	0/4 (0)	0/5 (0)	4/23 (17)

IVIG, intravenous immunoglobulin; NA, not applicable; URI, upper respiratory infection. [a]At the time of the first assessment at the hospital for respiratory tract symptoms. [b]Within 1 month of the onset of RSV infection.

patients, treatment was given between 1 and 12 days after microbiological diagnosis (median, 1 day) and between 1 and 22 days after the onset of the first symptom (median, 6 days). The 30-day survival analysis on progression to pneumonia for patients who presented to our center with an URI was calculated according to the early use of a ribavirin-based regimen. Of the 38 patients initially seen with an URI, 13 developed pneumonia. No death occurred during that period. Only one patient developed pneumonia despite receiving ribavirin at the URI stage (Figure 2). Five patients (10%) died within 30 days of RSV infection; all had pneumonia, and two had co-infections (influenza A infection in one and *Enterococcus faecium* bacteremia in the other). Autopsies were not performed on these patients.

On univariate analysis, risk factors for mortality at 30 days were age ≥65 years, longer duration of symptoms before the diagnosis of RSV infection (14 days), APACHE II score > 15 at the time of the first assess-

Figure 1. Outcome at 30 days of RSV-infected patients with leukemia according to the use of ribavirin therapy.



*p=0.1

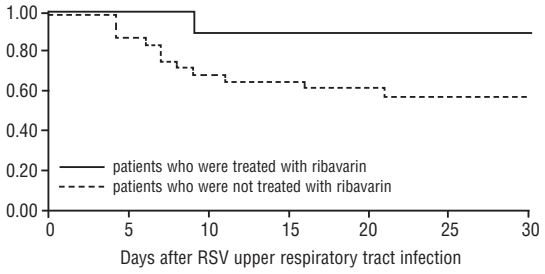


Figure 2. Kaplan-Meier survival curves of progression to pneumonia from URI in leukemia patients who presented with RSV URI and did (solid line) or did not (dotted line) receive a ribavirin-based regimen (p=0.095).

ment for respiratory symptoms, presence of comorbidities, and progression to pneumonia (all $p \leq 0.05$). Multivariate analysis failed to show any significant risk factor for a fatal outcome.

Discussion

Several important conclusions can be drawn from this study, the largest to date analyzing RSV infection in leukemia patients. First, RSV infection is an important cause of morbidity and mortality among patients with leukemia. Second, many RSV infections resolve uneventfully without therapy. However, we identified a subset of leukemia patients who are at increased risk of progression to pneumonia. Third, the use of a ribavirin-based regimen may halt such progression and reduce mortality.

We identified several risk factors for progression to pneumonia, such as high APACHE II score at the time of the first evaluation for respiratory symptoms, persistent lymphocytopenia, and corticosteroid use within 1 month of the onset of RSV infection. There was a trend toward a higher rate of progression to pneumonia in males than females. In healthy children, the rate of hospitalization for RSV infection for boys is approximately twice that for girls, indicating that the disease may be more severe in males.[20] In leukemia patients, the highest frequency of progression to pneumonia has been reported in patients with chemotherapy-induced myelosuppression.[8]

Once the neutrophil count recovers, these patients apparently have a better control of their RSV infections.[8] However, whether neutrophils themselves are important or are a surrogate marker for some other host defense mechanism is not known.[8] For example, neutropenic patients with leukemia have deficiencies in other host defense mechanisms, and most neutropenic patients with leukemia also have lymphocytopenia.[21] In our series, neutropenia was not significantly associated with progression to pneumonia, whereas persistent lymphocytopenia seemed to be related to such an event, in accordance with previous observations in HSCT recipients.[5] Additional risk factor for developing RSV pneumonia need to be identified in studies including larger numbers of leukemia patients.

Although we found that many RSV infections resolve uneventfully without therapy, we also found that certain subgroups of patients with RSV infection would benefit from treatment with antiviral therapy. Treating all leukemia patients with RSV-associated URIs would be impractical, given the cost and discomfort of ribavirin aerosol administration with its potentially serious side effects, and hazards to health care workers.[22] However, our findings indicate that in some subsets of leukemia patients at risk of developing pneumonia, such as males, patients with a high APACHE II score, patients with prolonged lymphocytopenia, or those who have recently used corticosteroids, pre-emptive therapy for URI should be considered to halt progression of pneumonia. Similarly, our data suggest that patients who have developed RSV pneumonia may still benefit from ribavirin therapy.

Non-randomized trials in HSCT recipients have shown that the use of aerosolized ribavirin plus IVIG is associated with more favorable outcomes than those seen previously in patients with RSV pneumonia, especially when treatment is initiated early during the infection.[1-4, 11, 13, 23, 24]

In this population, the prompt use of such combination treatment resulted in a dramatic decrease in the overall mortality rate from 100% to less than 40%.[1, 2, 12, 13] However, some non-controlled studies suggest that ribavirin may not be necessary for treating RSV infection among HSCT recipients (mainly recipients of autologous transplants) because some RSV-infected patients, including patients with RSV pneumonia, have a good outcome without treatment.[14, 15, 25] The reasons for these discrepancies are poorly understood but are likely due to the immune status of the patient at the time of infection, or to differences in virulence between circulating RSV strains. In the first randomized, controlled trial in HSCT recipients, the use of ribavirin seemed to be associated with less clinically and virologically proven RSV pneumonia, as well as a decrease in RSV load in the respiratory tract.[16] These results were not, however, statistically significant, probably due to the small number of patients evaluated (n=14).

Likewise, there have been conflicting results from studies of aerosolized ribavirin in leukemia patients.[7, 8, 15, 19] Most of these studies suffer from relatively small sample size (< 20 patients). Abdallah *et al.* reported on five patients with leukemia who developed RSV

infection (pneumonia in four). None of them received ribavirin therapy, and they all survived.[15] In contrast, previous data on leukemia patients with RSV pneumonia seen at our center suggest that prompt therapy with aerosolized ribavirin and IVIG at an early stage of pneumonia is associated with improved outcomes.[8] Specifically, none of eight patients in whom therapy was initiated more than 24 hours prior to intubation died, whereas the mortality rate was 89% among patients who received no therapy (n = 3), began therapy after the onset of respiratory failure (n = 4), or were unable to tolerate the therapy (n = 2).[8] In the current study, we assessed a sizeable number of patients with leukemia (n=52), and we found that therapy for RSV URI might have prevented progression to pneumonia and might improve outcome. One of the nine patients in whom ribavirin therapy was initiated during the URI stage of infection experienced progression to pneumonia, and none had died by 30 days. In contrast, 26 of the 43 patients who received no therapy or in whom therapy was not initiated during the URI stage of infection developed pneumonia, and five died. On the other hand, in a subset analysis of patients who presented to our center with RSV URI only, we still found a trend in progression to pneumonia in patients who did not receive therapy with aerosolized ribavirin (Figure 2).

Ribavirin is often combined with IVIG or high-titer RSV immunoglobulins for therapy in HSCT recipients.[11,26] In addition, palivizumab, a RSV-specific monoclonal antibody, has become available for prophylaxis of RSV infection in patients at risk, and some physicians are using it in combination with ribavirin, primarily in HSCT recipients.[27] The benefit of combining aerosolized ribavirin with IVIG in leukemia recipients remains to be elucidated in prospective controlled clinical trials, as does the benefit of using standard IVIG preparations rather than antibody preparations containing high titers of RSV-neutralizing antibody or RSV-specific monoclonal antibody.[24, 27]

Our data should be interpreted with caution because of the retrospective nature of our study. It is possible that our data underestimate true RSV-related morbidity and mortality, particularly among patients who did not seek medical attention for minimal respiratory symptoms. A quantitative assay could have more value for detecting RSV in respiratory specimens and evaluating the efficacy of antiviral therapy.[16] There were no definite criteria for prescribing antiviral therapy and such therapy was initiated at the discretion of the treating physician. Therefore, data regarding the efficacy of aerosolized ribavirin therapy were analyzed in a non-controlled manner. However, based on a recent experience in HSCT recipients,[16] carrying out a controlled randomized study to asses the efficacy of aerosolized ribavirin against RSV infection in leukemia patients will be impracticable and probably unfeasible.

In summary, RSV pneumonia in leukemia patients is associated with significant morbidity and mortality. Our data suggest that in some subsets of leukemia patients with RSV infection, the use of ribavirin when the RSV infection is still confined to the upper respiratory tract might prevent progression to pneumonia and death.

Authors' Contributions

RFC: designed the research; RFC, HAT, EAA, and CAS performed the clinical research; RFC and HAT controlled and analyzed the data; NR and YJ performed the statistical analysis, HAT, and RFC wrote the paper; GNM, MEC, AS, HMK, and IIR helped analyzing the data and critically reviewing the manuscript and all authors checked the final version of the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

1. Chemaly RF, Ghosh S, Bodey GP, Rohatgi N, Safdar A, Keating MJ, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 2006;85:278-87.
2. Hicks KL, Chemaly RF, Kontoyiannis DP. Common community respiratory viruses in patients with cancer: more than just *common colds*. Cancer 2003; 97:2576-87.
3. Whimbey E, Ghosh S. Respiratory syncytial virus infections in immunocompromised adults. Curr Clin Top Infect Dis 2000;20:232-55.
4. Whimbey E, Champlin RE, Couch RB, Englund JA, Goodrich JM, Raad I, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22:778-82.
5. Ljungman P, Ward KN, Crooks BN, Parker A, Martino R, Shaw PJ, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2001;28:479-84.
6. Machado CM, Boas LS, Mendes AV, Santos MF, da Rocha IF, Sturaro D, et al. Low mortality rates related to respiratory virus infections after bone marrow transplantation. Bone Marrow Transplant 2003;31:695-700.
7. Ebbert JO, Limper AH. Respiratory syncytial virus pneumonitis in immunocompromised adults: clinical features and outcome. Respiration 2005;72:263-9.
8. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. Am J Med 1997; 102:10-8; discussion 25-6.
9. Ljungman P. Respiratory virus infections in bone marrow transplant recipients: the European perspective. Am J Med 1997;102:44-7.
10. Harrington RD, Hooton TM, Hackman RC, Storch GA, Osborne B, Gleaves CA, et al. An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis 1992;165:987-93.
11. Small TN, Casson A, Malak SF, Boulad F, Kiehn TE, Stiles J, et al. Respiratory syncytial virus infection following hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;29:321-7.
12. Whimbey E, Champlin RE, Englund JA, Mirza NQ, Piedra PA, Goodrich JM, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syn-

cytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 1995;16:393-9.
13. Champlin RE, Whimbey E. Community respiratory virus infections in bone marrow transplant recipients: the M.D. Anderson Cancer Center experience. Biol Blood Marrow Transplant 2001;7 Suppl:8S-10S.
14. Anaissie EJ, Mahfouz TH, Aslan T, Pouli A, Desikan R, Fassas A, et al. The natural history of respiratory syncytial virus infection in cancer and transplant patients: implications for management. Blood 2004;103: 1611-7.
15. Abdallah A, Rowland KE, Schepetiuk SK, To LB, Bardy P. An outbreak of respiratory syncytial virus infection in a bone marrow transplant unit: effect on engraftment and outcome of pneumonia without specific antiviral treatment. Bone Marrow Transplant 2003;32:195-203.
16. Boeckh M, Englund J, Li Y, Miller C, Cross A, Fernandez H, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. Clin Infect Dis 2007;44:245-9.
17. Whimbey E, Couch RB, Englund JA, Andreeff M, Goodrich JM, Raad II, et al. Respiratory syncytial virus pneumonia in hospitalized adult patients with leukemia. Clin Infect Dis 1995; 21:376-9.
18. Field K, Slavin MA, Seymour JF. Severe respiratory syncytial virus pneumonia complicating fludarabine and cyclophosphamide treatment of chronic lymphocytic leukemia. Eur J Haematol 2002;69:54-7.
19. Eftekhari P, Lassoued K, Oksenhendler E, Scieux C, Clauvel JP. Severe respiratory syncytial virus pulmonary infection in a patient treated with fludarabine for chronic lymphocytic leukemia. Ann Hematol 1998;76:225-6.
20. Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care 2003;48:209-31; discussion 31-3.
21. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64: 328-40.
22. Shults RA, Baron S, Decker J, Deitchman SD, Connor JD. Health care worker exposure to aerosolized ribavirin: biological and air monitoring. J Occup Environ Med 1996;38: 257-63.
23. Ghosh S, Champlin RE, Englund J, Giralt SA, Rolston K, Raad I, 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;25:751-5.
24. Ghosh S, Champlin RE, Ueno NT, Anderlini P, Rolston K, Raad I, et al. Respiratory syncytial virus infections in autologous blood and marrow transplant recipients with breast cancer: combination therapy with aerosolized ribavirin and parenteral immunoglobulins. Bone Marrow Transplant 2001;28:271-5.
25. Aslan T, Fassas AB, Desikan R, Siegel D, Munshi N, Mehta J, et al. Patients with multiple myeloma may safely undergo autologous transplantation despite ongoing RSV infection and no ribavirin therapy. Bone Marrow Transplant 1999;24:505-9.
26. DeVincenzo JP, Hirsch RL, Fuentes RJ, Top FH, Jr. Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation - a compassionate use experience. Bone Marrow Transplant 2000;25:161-5.
27. Boeckh M, Berrey MM, Bowden RA, Crawford SW, Balsley J, Corey L. Phase 1 evaluation of the respiratory syncytial virus-specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. J Infect Dis 2001;184:350-4.