Biol Blood Marrow Transplant 19 (2013) 589–596

Outcome of Respiratory Syncytial Virus Lower Respiratory Tract Disease in Hematopoietic Cell Transplant Recipients Receiving Aerosolized Ribavirin: Significance of Stem Cell Source and Oxygen Requirement

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Article history:
Received 27 November 2012
Accepted 21 December 2012

Key Words:
Respiratory syncytial virus
Lower respiratory tract disease
Palivizumab
Pulmonary function
Hematopoietic cell transplantation

A B S T R A C T

Respiratory syncytial virus (RSV) infection is an important complication after hematopoietic cell transplantation (HCT), and RSV lower respiratory tract disease (LRD) results in substantial early mortality and late airflow obstruction among survivors. Factors associated with poor outcome are unknown. We evaluated the effect of transplant and treatment factors on overall survival, mortality from respiratory failure, and pulmonary function among 82 HCT recipients who had RSV LRD between 1990 and 2011. All patients received aerosolized ribavirin. In multivariable analyses, only the use of marrow or cord blood as graft source (adjusted hazard ratio [aHR], 4.1; 95% confidence interval [CI], 1.8 to 9.0; $P < .001$) and oxygen requirement (aHR, 3.3; 95% CI, 1.5 to 6.7; $P = .003$) remained independently associated with overall mortality and death due to respiratory failure (aHR, 4.7; 95% CI, 1.8 to 13; $P = .002$ and aHR, 5.4; 95% CI, 1.8 to 16; $P = .002$, respectively). Antibody-based treatments, including intravenous immunoglobulin and palivizumab, were not independently associated with improved outcome and did not alter the associations of the graft source and oxygen requirements in statistical models. In conclusion, use of peripheral blood stem cells as graft source and lack of oxygen requirement at diagnosis appear to be important factors associated with improved survival of HCT recipients with RSV LRD. These results may explain differences in outcomes reported from RSV infection over time and may guide the design of future interventional trials.

INTRODUCTION

Respiratory syncytial virus (RSV), known as a major cause of seasonal respiratory viral infection, can cause lower respiratory tract disease (LRD) in patients after hematopoietic cell transplantation (HCT). RSV infection in this population results in substantial early mortality and has been associated with late airflow decline [1-5]. Outcome studies are often small in size, and results are difficult to interpret across sites because factors associated with outcome have not been well defined [6-9]. Candidate variables from smaller series of respiratory virus disease as well as studies with other serious pathogens such as aspergillus suggested a role of lymphopenia, mechanical ventilation, corticosteroids, copathogens and immune-based therapies on the outcome [6,10,11].

The purpose of this retrospective study was to examine the impact of transplant- and treatment-related factors on overall survival, mortality from respiratory failure, and the degree of pulmonary function decline in a large cohort of HCT recipients who received aerosolized ribavirin for RSV disease.

METHODS

Study Design

This was a retrospective cohort study in which patients with RSV LRD during pretransplantation conditioning or after HCT at the Fred Hutchinson Cancer Research Center from January 1990 to April 2011 were evaluated. RSV LRD was defined as detection of RSV by shell vial centrifugation culture, direct fluorescent antibody tests, or conventional culture using a bronchoalveolar lavage specimen (n = 79), lung biopsy sample (n = 2), or tracheal mucus (n = 1), accompanied with lower respiratory tract symptoms and/or abnormal radiographic findings [7]. More recent patients were also positive by polymerase chain reaction.

All patients were treated with aerosolized ribavirin (6 g given as a single dose over 16 hours or 2 g three times daily over 2 hours) [12]. Patients who did not receive ribavirin (n = 17), who received oral or intravenous ribavirin (n = 12), or who received RSV-specific polyclonal immunoglobulin (n = 5) were excluded. Intravenous immunoglobulin (IVIG) for treatment (500 mg/kg three times weekly) was given at the attending physician's discretion. Replacement IVIG was given when the level of IgG dropped to <400 mg/dL.

Palivizumab was given to 12 subjects as part of a research study before U.S. Food and Drug Administration approval [13]. After the drug became commercially available (1999), we instituted a guideline to routinely administer palivizumab for RSV LRD in combination with aerosolized ribavirin (starting in 2002). A single dose of palivizumab (15 mg/kg ideal body weight) was administered intravenously, except in 1 patient who received 2 doses. This study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Definitions

Underlying disease risk groups at transplantation were classified as either standard or high risk. The high-risk group was defined as acute leukemia, chronic lymphoid leukemia, lymphoma, multiple myeloma, and solid tumor not in remission, chronic myeloid leukemia in blast crisis, and all relapsed diseases after HCT. All other stages in any disease as well as myelodysplastic syndrome were categorized into the standard-risk group.

Financial disclosure: See Acknowledgments on page 595.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2012.12.019

Myeloablative conditioning regimens mainly consisted of high-dose cyclophosphamide and busulfan or fractionated total body irradiation (12.0 or 13.2 Gy). Reduced-intensity conditioning regimens consisted of fludarabine with a single fraction of total body irradiation (2 Gy). A copathogen was defined as a significant pathogen detected by culture or direct staining methods obtained from bronchoalveolar lavage specimens or lung biopsy samples. Death due to respiratory failure was defined as any death caused exclusively or predominantly by respiratory failure.

Pulmonary Function Testing and Bronchiolitis Obliterans Syndrome

All but 5 patients had undergone pulmonary function testing (PFT) before the diagnosis of RSV LRD, and these values, mostly before HCT, were used as baseline values. PFT values after LRD included PFTs obtained at day 60 ± 25 days (early post-LRD) and day 365 ± 90 days (late post-LRD). All PFTs were performed in accordance with American Thoracic Society guidelines [14]. Predicted values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity of the lung for carbon monoxide (DL_{CO}) were determined using published equations for children and adults. All DL_{CO} measurements were corrected for hemoglobin values. Based on the modified National Institutes of Health (NIH) guidelines, airflow obstruction was defined as FEV1/FVC < .7, FEV1 < 75%, and FEV1 decrease of ≥10% from pre-RSV LRD value [15,16].

Patients with bronchiolitis obliterans syndrome (BOS) were identified according to the modified NIH diagnostic criteria: (1) FEV1/FVC <.7, (2) FEV1 < 75%, (3) FEV1 decrease of ≥10% from pretransplantation value, (4) residual volume >120% of predicted normal or evidence of air trapping, and (5) absence of respiratory tract infection or pathologic confirmation [15-17].

Statistical Analysis

Patients were analyzed based on their first episode of RSV LRD. The Wilcoxon rank sum test was used to compare the change of PFT values before and after RSV LRD. The probability of overall survival was estimated with the use of the Kaplan-Meier method. The probability of mortality due to respiratory failure was estimated by cumulative incidence curves, with death from other reasons as a competing risk. The log-rank test was used for the comparison between curves. Cox proportional hazards models were used to evaluate unadjusted and adjusted hazard ratios (HRs) for overall mortality and mortality due to respiratory failure as well as associated 95% confidence intervals (CIs).

Use of palivizumab or IVIG was treated as a time-dependent variable. Covariates evaluated as candidates for risk factors in the multivariable models included transplantation year, stem cell source, donor type, conditioning regimen, white blood cell count, copathogens, oxygen use at diagnosis, ribavirin use prediagnosis, and antibody-based treatment. Variables with $P \leq .1$ in the univariate models were candidates for multivariable models. Antibody-based treatments were included into the final models regardless of level of significance in the univariate analysis. Two-sided P values <.05 were considered to be statistically significant. All statistical analyses were performed using SAS 9.2 for Windows (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 82 patients with RSV LRD who received aerosolized ribavirin were evaluated. Characteristics of all patients and the patients receiving PFTs are outlined in Table 1. The median time to LRD after HCT was 54.5 days (range, −1 to 2058 days), and the median recipient age was 43 years (range, 3 to 68).

Outcomes

Among all 82 patients, 26 (32%) and 35 (43%) died from any cause by day 30 and day 100 after RSV LRD, respectively. Deaths due to respiratory failure by day 30 and day 100 after RSV LRD were observed in 18 (22%) and 24 (29%) patients, respectively. The probabilities of overall survival and of death due to respiratory failure at day 100 after RSV LRD according to transplantation year are shown in Figure 1A,B. Patients undergoing HCT in and after 1997 showed an improved outcome, although the differences did not reach statistical significance (overall survival, $P = .074$; death due to respiratory failure, $P = .283$) (Figure 1A,B).

Table 1
Characteristics of Patients with RSV LRD

	All Patients (n = 82)	Patients Receiving PFT (n = 28)
Gender		
Male	48 (59)	14 (50)
Female	34 (41)	14 (50)
Age at RSV LRD, year		
≤20	6 (7)	2 (7)
21-60	68 (83)	25 (89)
>60	8 (10)	1 (4)
Days between transplantation and RSV LRD		
≤30	34 (41)	14 (50)
31-365	39 (48)	13 (46)
>365	9 (11)	1 (4)
Transplantation year		
1989-1996	24 (29)	5 (18)
1997-2001	33 (40)	15 (53)
2002-2010	25 (31)	8 (29)
Disease risk		
Standard	48 (59)	16 (57)
High	34 (41)	12 (43)
Stem cell source		
Peripheral blood stem cell	37 (45)	15 (54)
Bone marrow	41 (50)	11 (39)
Cord blood	4 (5)	2 (7)
Donor type		
Autologous	15 (18)	2 (6)
HLA-matched related	25 (30)	9 (32)
HLA-matched unrelated	21 (26)	8 (29)
HLA-mismatched	21 (26)	9 (32)
Conditioning regimen		
MA + TBI (> 12Gy)	45 (55)	19 (68)
MA ± low TBI	23 (28)	4 (14)
Reduced-intensity conditioning	14 (17)	5 (18)
%FEV1/FVC pre RSV LRD		
≥70	60 (78)	22 (79)
<70	17 (22)	6 (21)
%TLC pre RSV LRD		
≥80	66 (90)	26 (96)
<80	7 (10)	1 (4)
White blood cell counts		
>1000 × 106/L	51 (62)	19 (68)
≤1000 × 106/L	31 (38)	9 (32)
Lymphocyte count		
>500 × 106/L	19 (23)	7 (25)
100-500 × 106/L	38 (46)	14 (50)
<100 × 106/L	25 (31)	7 (25)
Copathogen		
None	54 (66)	20 (71)
Any pathogen	23 (28)	6 (22)
Multiple pathogens	5 (6)	2 (7)
Oxgen at diagnosis		
None	33 (42)	12 (44)
≤2L/minute	12 (15)	7 (26)
>2L/minute	26 (33)	7 (26)
Mechanical ventilation	8 (10)	1 (4)
Steroid use at diagnosis		
None	38 (46)	12 (43)
<1 mg/kg	25 (30)	9 (32)
≥1 mg/kg	19 (23)	7 (25)
Ribavirin use prediagnosis		
None	56 (68)	15 (53)
<5 days	10 (12)	5 (18)
≥5 days	16 (20)	8 (29)
Intravenous immunoglobulin		
None	43 (53)	16 (57)
Low-dose*	19 (23)	7 (25)
High-dose	20 (24)	5 (18)
Palivizumab		
Yes	38 (46)	15 (54)
No	44 (54)	13 (46)

MA indicates myeloablative conditioning; TBI, total body irradiation; %TLC, percentage of predicted total lung capacity.
All values are indicated as the number (percentage).
* To maintain levels of >400 mg/dl, as needed.

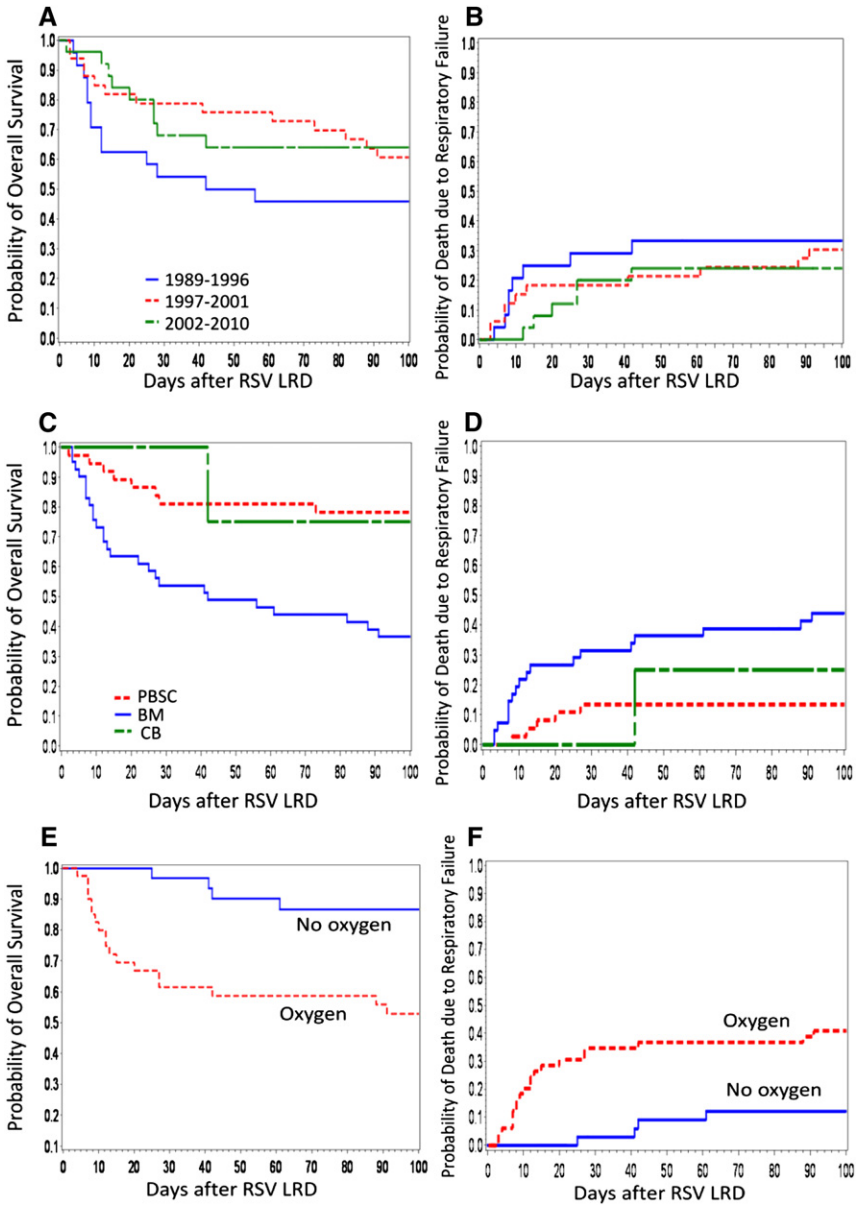

Figure 1. (A) Kaplan-Meier estimate of overall survival according to transplantation year in HCT recipients after RSV LRD ($P = .256$, for 3-group comparison). (B) Cumulative incidence of death due to respiratory failure according to transplantation year ($P = .605$). (C) Kaplan-Meier estimate of overall survival according to stem cell source in HCT recipients after RSV LRD ($P < .001$). (D) Cumulative incidence of death due to respiratory failure according to stem cell source ($P = .006$). (E) Kaplan-Meier estimate of overall survival according to the oxygen requirement at diagnosis in HCT recipients after RSV LRD ($P = .001$). (F) Cumulative incidence of death due to respiratory failure according to the oxygen requirement at diagnosis ($P = .002$).

Risk Factors for Mortality from All Causes or Respiratory Failure by 100 Days after RSV LRD

Univariate analyses of risk factors for overall mortality identified that the use of bone marrow (BM) as stem cell source, baseline oxygen requirement of more than 2 L/min, and white blood cell count of 1000 $\times$ 10^6/L or less at diagnosis are significantly correlated with high mortality (Table 2). The results for death due to respiratory failure were similar. Multivariable analyses demonstrated that only the use of BM or cord blood (CB) as stem cell source and oxygen requirement remained associated with increased overall mortality and death due to respiratory failure (Table 3), which was confirmed in the cohort excluding the 4 patients receiving CB (data not shown).

Overall survival and mortality due to respiratory failure according to these 2 factors are shown in Figure 2. Day-100 mortality due to respiratory failure among peripheral blood stem cell transplantation (PBSCT) recipients without oxygen was 0%, whereas among BM or CB transplantation (BMT/CBT) recipients who received oxygen, overall mortality was 58% (Figure 2B). A total of 24 patients required mechanical ventilation during the clinical course of RSV LRD (including 8 at the time of diagnosis), and 15 of them died from respiratory failure by 100 days after RSV LRD. All 4 BMT/CBT recipients requiring mechanical ventilation at diagnosis died, compared with 1 of 4 PBSCT recipients (Figure 2C,D).

To examine whether the use of antibody-based treatments were independently associated with these 2 outcomes

Table 2
Univariate Analysis of Risk Factors for Mortality from All Causes or Respiratory Failure by Day 100 after RSV LRD

	Overall Mortality			Mortality from Respiratory Failure		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Transplantation year						
1989-1996	1.00			1.00		
1997-2001	0.59	0.3-1.3	.180	0.75	0.3-1.9	.548
2002-2010	0.54	0.2-1.3	.155	0.59	0.2-1.7	.327
Stem cell source						
Peripheral blood stem cell	1.00			1.00		
Bone marrow	3.94	1.8-8.7	<.001	4.31	1.6-12	.004
Cord blood	1.07	0.1-8.6	.947	1.71	0.2-15	.626
Donor type						
Autologous	1.00			1.00		
Allogeneic	1.91	0.7-5.4	.222	5.60	0.8-42	.092
Conditioning regimen						
MA + TBI (≥12 Gy)	1.00			1.00		
MA ± low TBI	0.78	0.4-1.7	.524	0.34	0.1-1.1	.081
Reduced-intensity conditioning	0.50	0.2-1.4	.199	0.64	0.2-1.9	.424
White blood cell counts						
$>1000 \times 10^6$/L	1.00			1.00		
$\leq 1000 \times 10^6$/L	2.29	1.2-4.4	.015	2.16	1.0-4.8	.060
Copathogen						
None	1.00			1.00		
Any pathogen	1.36	0.7-2.8	.406	0.80	0.3-2.2	.671
Multiple pathogens	1.83	0.5-6.1	.331	2.35	0.7-8.1	.177
Oxygen at diagnosis						
None	1.00			1.00		
≤2L/minute	0.71	0.2-3.3	.656	1.58	0.3-8.7	.596
>2L/minute	3.13	1.4-7.1	.006	5.15	1.7-16	.005
Mechanical ventilation	6.21	2.2-18	<.001	11.2	3.0-42	<.001
Ribavirin use pre diagnosis						
None	1.00			1.00		
<5 days	0.67	0.2-1.9	.450	0.23	0.0-1.7	.148
≥5 days	0.43	0.2-1.2	.120	0.44	0.1-1.5	.191
Ab-based treatment as time-dependent variable						
None/Low-dose	1.00			1.00		
High-dose	1.17	0.5-2.8	.727	1.41	0.5-3.9	.510
Palivizumab*	0.74	0.3-1.6	.450	0.76	0.3-2.0	.567

MA indicates conditioning; TBI, total body irradiation; Ab, antibody; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; %TLC, percentage of predicted total lung capacity; GVHD, graft-versus-host disease; CMV, cytomegalovirus.
All variables in Table 1 were used for the univariate analysis. Only variables with $P < .2$ in any analysis, except for Ab-based treatment, are shown in this table. The following parameters were not significantly associated: gender, age at RSV LRD, days between transplantation and RSV LRD, diagnosis, disease risk at transplantation, %FEV1/FVC pre-RSV LRD, %TLC pre-RSV LRD, lymphocyte count, steroid use at diagnosis, GVHD prophylaxis, recipient CMV serostatus, and GVHD in lung at RSV LRD.
* This includes 2 patients who received both palivizumab and high-does intravenous immunoglobulin.

and/or whether they altered the effect of the stem cell source and oxygen requirements, we fit several multivariable models (Table 3). None of these models showed an independent effect of antibody-based treatments or a significant change in the effect size of the 2 major risk factors. Additional models were fit including oxygen levels >2 L or mechanical ventilation and mechanical ventilation alone, none of which showed qualitatively different results (data not shown). Subset analyses restricting the patients transplanted between 1997 and 2010, which would decrease the effect of a time bias, also did not reveal different results (Table 4). The effect of the receipt of PBSC and lack of oxygen

Table 3
Multivariable Analysis of Risk Factors and Treatment Efficacy for Mortality from All Causes or Respiratory Failure by Day 100 after RSV LRD

	Overall Mortality			Mortality from Respiratory Failure		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Model 1						
Stem cell source						
Peripheral blood stem cell	1.00			1.00		
Bone marrow/Cord blood	4.08	1.8-9.0	<.001	4.73	1.8-13	.002
Oxygen at diagnosis						
No	1.00			1.00		
Yes	3.12	1.5-6.7	.003	5.39	1.8-16	.002
Model 2						
Ab-based treatment as time-dependent variable						
None/Low-dose	1.00			1.00		
High-dose	1.75	0.7-4.2	.216	2.15	0.8-6.1	.148
Palivizumab*	1.04	0.5-2.3	.920	1.10	0.4-2.9	.843
Stem cell source						
Peripheral blood stem cell	1.00			1.00		
Bone marrow/Cord blood	3.86	1.7-8.7	.001	4.44	1.6-12	.004
Model 3						
Ab-based treatment as time-dependent variable						
None/Low-dose	1.00			1.00		
High-dose	1.75	0.7-4.3	.221	2.42	0.9-6.9	.097
Palivizumab*	0.99	0.4-2.2	.974	1.07	0.4-2.8	.888
Oxygen at diagnosis						
No	1.00			1.00		
Yes	2.94	1.3-6.5	.008	5.39	1.8-16	.003

Ab indicates antibody.
The factors with $P < .1$ in Table 2 were evaluated in the multivariable models; Ab-based treatments were included regardless of level of significance in the univariate models.
* This includes 2 patients who received both palivizumab and high-does intravenous immunoglobulin.

requirement at diagnosis on overall survival and death due to respiratory failure are shown in Figure 1C-F.

Changes in Pulmonary Function and BOS

Among the 82 patients, 28 were examined for pulmonary function at 60 days and/or 1 year after RSV LRD. Most of the PFT values declined within 2 months after infection; for some parameters, the decline continued for 1 year (Figure 3). In $\%DL_{co}$, the decrease was significant at 60 days after RSV LRD ($P = .003$). The modified NIH criteria for airflow obstruction were met in 2 of 21 patients at 60 days after RSV LRD and in 2 of 16 patients at 1 year. Among the 82 patients, 5 were diagnosed as BOS according to the modified NIH diagnostic criteria. Four of them had BOS before RSV LRD, whereas only 1 developed BOS 9 months after RSV LRD.

DISCUSSION

This retrospective cohort study of RSV LRD found that a favorable outcome is significantly associated with the use of PBSC as a graft source and the absence of requiring oxygen at the time of diagnosis of RSV LRD. The importance of respiratory failure at the time of diagnosis on subsequent clinical outcome has been suggested by other studies [11]. Because oxygen use at diagnosis may serve as a surrogate indicator of acute lung injury, this observation is plausible. Perhaps the most important and novel finding in this report is that patients after PBSCT had a lower mortality and death

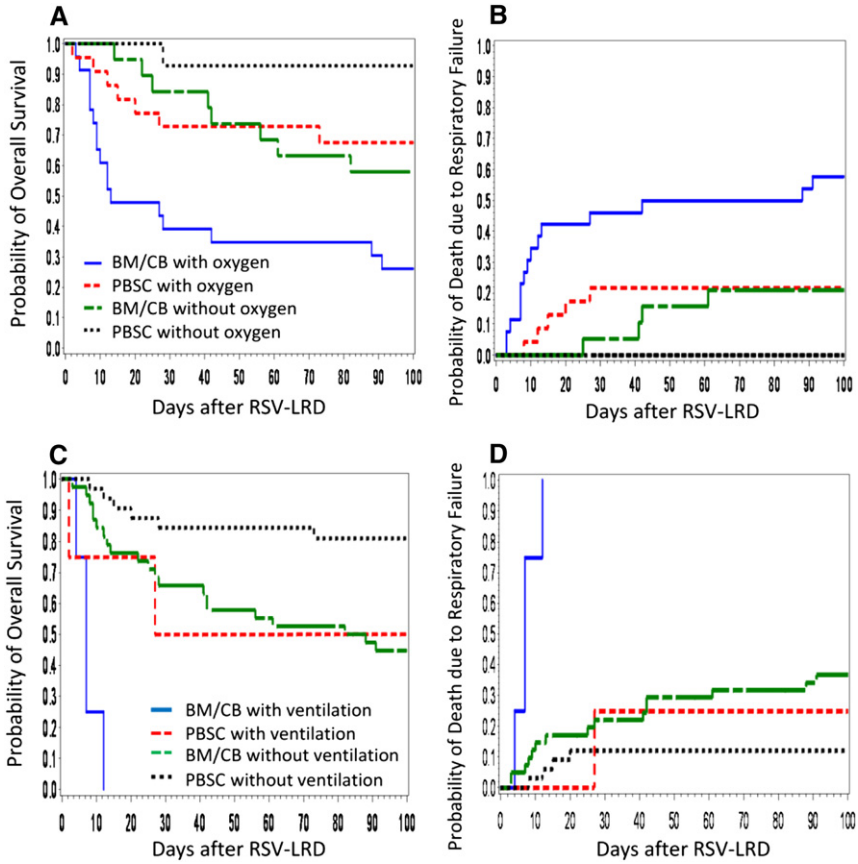

Figure 2. (A) Kaplan-Meier estimate of overall survival according to stem cell source and the oxygen requirement at diagnosis ($P \leq .0001$, for 4-group comparison). (B) Cumulative incidence of death due to respiratory failure according to stem cell source and the oxygen requirement at diagnosis ($P \leq .0001$). (C) Kaplan-Meier estimate of overall survival according to stem cell source and mechanical ventilation requirement at diagnosis ($P \leq .0001$). (D) Cumulative incidence of death due to respiratory failure according to stem cell source and mechanical ventilation requirement at diagnosis ($P \leq .0001$).

from respiratory failure than those who had received BMT or CBT. Previous studies demonstrated that patients after PBSCT have higher numbers of adoptively transferred lymphocytes and earlier immune reconstitution, resulting in fewer infections compared with those after BMT [10,18-20]. Although only very few CBT recipients were included in this analysis, CBT is also known to have late immune reconstitution compared with PBSCT or BMT [21-24]. Our observation that PBSCT recipients have improved survival after documented RSV LRD suggests that the degree of immunosuppression is a key factor in the recovery from the disease.

Interestingly, other factors, such as lymphopenia at the time of diagnosis, the presence of copathogens, baseline lung function, and antibody treatments, did not appear to be important in this study. Although palivizumab has shown a proven prophylactic effect in infants at high risk for bronchiolitis, little is known about the treatment efficacy of palivizumab in adults and HCT recipients with RSV LRD. Some studies have suggested an improved outcome of RSV infection after palivizumab treatment; however, the drug is not approved for this indication, and most studies have been small and nonrandomized, thereby limiting the ability to perform multivariable analyses [3,11,25-28]. The current study suggests that PBSC and more frequent diagnosis of RSV LRD at a stage before oxygen dependency, rather than palivizumab, was likely the important factor in the improved outcome of RSV disease in recent years. Although Ottolini et al. demonstrated that palivizumab can reduce viral replication in lung in an animal model, the complete control of viral replication required sequential use of multiple doses of palivizumab [29]. Likewise, intubated infants with RSV infection showed reduced RSV titers in tracheal aspirates after palivizumab treatment; however, clinical outcomes were not affected [30].

Based on these data, we speculate that once RSV-attributed airway inflammation begins [5], palivizumab alone may not be able to interfere with the inflammatory cascade. In the setting of prophylaxis of RSV LRD, palivizumab reduced respiratory symptoms, including wheezing, in premature infants [31]. Therefore, the use of palivizumab before progression to LRD might theoretically be beneficial to prevent pulmonary function decline. At this point, such an effect is hypothetical, and randomized trials are needed to answer these questions. The development of newer, more potent RSV monoclonal antibodies such as motavizumab could potentially be of interest in future studies, although this new monoclonal was not approved by the U.S. Food and Drug Administration after trials in high-risk infants [32,33], and a recent study suggested no benefit in the treatment setting [34].

The decline in pulmonary function is one of the important features of RSV LRD [5]. Previous studies have suggested that respiratory virus infections after lung transplantation stimulate the incidence of BOS [35-38]. Compared with the incidence rates of BOS (2% to 6%) in recent studies based on the new NIH diagnostic criteria [17,39], the incidence in our

Table 4
Risk Factors for Mortality from All Causes or Respiratory Failure by Day 100 after RSV LRD in Patients Transplanted between 1997 and 2010 (n = 58)

Risk Factors	Overall Mortality						Mortality from Respiratory Failure					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Transplantation year												
1997-2001	1.00						1.00					
2002-2010	0.95	0.4-2.2	.907				0.81	0.3-2.2	.686			
Stem cell source												
Peripheral blood stem cell	1.00			1.00			1.00			1.00		
Bone marrow	3.77	1.5-9.4	.004	4.71	1.9-12	.001	5.16	1.6-16	.005	7.76	2.4-25	<.001
Cord blood	1.06	0.1-8.6	.956				1.85	0.2-17	.581			
Conditioning regimen												
MA + TBI (≥12 Gy)	1.00						1.00					
MA ± low TBI	0.83	0.3-2.3	.725				0.20	0.0-1.5	.118			
Reduced-intensity conditioning	0.78	0.3-2.4	.670				0.91	0.3-2.9	.867			
White blood cell counts												
$>1000 \times 10^6$/L	1.00						1.00					
$\leq 1000 \times 10^6$/L	1.86	0.8-4.3	.147				1.76	0.7-4.7	.262			
Copathogen												
None	1.00						1.00					
Any pathogen	1.10	0.4-2.9	.843				0.71	0.2-2.6	.601			
Multiple pathogens	2.22	0.6-7.8	.214				2.81	0.8-10	.118			
Oxygen at diagnosis*												
None	1.00			1.00			1.00			1.00		
≤2L/minute	0.51	0.1-4.2	.532				1.19	0.1-12	.878			
>2L/minute	3.24	1.2-8.8	.020	3.57	1.4-9.0	.007	6.57	1.7-25	.006	7.98	2.2-29	.001
Mechanical ventilation	3.58	0.9-14	.065				5.59	0.9-34	.060			
Steroid use at diagnosis												
None	1.00						1.00					
<1 mg/kg	0.80	0.3-2.1	.645				0.94	0.3-3.1	.913			
≥1 mg/kg	2.00	0.7-5.9	.208				3.19	1.0-11	.057			
Ribavirin use prediagnosis												
None							1.00					
<5 days							0.37	0.1-2.8	.338			
≥5 days							0.25	0.0-1.9	.180			
Ab-based treatment as time-dependent varable												
None/Low-dose	1.00						1.00					
High-dose	1.49	0.4-6.0	.575				1.19	0.3-5.3	.824			
Palivizumab†	1.11	0.4-3.4	.856				0.77	0.2-2.5	.671			

MA indicates myeloablative conditioning; TBI, total body irradiation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; %TLC, percentage of predicted total lung capacity; GVHD, graft-versus-host disease; CMV, cytomegalovirus.
All variables in Table 1 were used for the univariate analysis. Only variables with $P < .2$ in any analysis are shown in this table. The following parameters were not significantly associated: gender, age at RSV LRD, days between transplantation and RSV LRD, donor type, diagnosis, disease risk at transplantation, GVHD prophylaxis, recipient CMV serostatus, and GVHD in lung at RSV LRD, %FEV1/FVC pre-RSV LRD, %TLC pre-RSV LRD, lymphocyte count. The factors with $P < .1$ were evaluated in the multivariable models.

* In the multivariate analysis, oxgen at diagnosis was categorized into 2 groups: none + ≤2L/minute and >2L/minute + mechanical ventilation.

† This includes 2 patients who received both palivizumab and high-dose intravenous immunoglobulin.

study was relatively high (10%; 5 among 50 allogeneic HCT recipients surviving more than 100 days after HCT). However, considering that our sample size is small and most patients were diagnosed with BOS before RSV LRD, we have insufficient information to make definitive conclusions about the association between BOS and RSV LRD.

Our study has strengths and limitations. It includes the largest outcome cohort of RSV LRD thus far with standardized diagnostic criteria (virologically proven LRD by conventional methods) and uniform antiviral treatment. Antibody-based treatments were protocol based for palivizumab but were given according to the attending physician's discretion for IVIG. The nonrandomized nature of the study is the most important limitation. However, conducting randomized trials is very difficult for rare diseases such as RSV LRD in HCT recipients and has failed in several instances

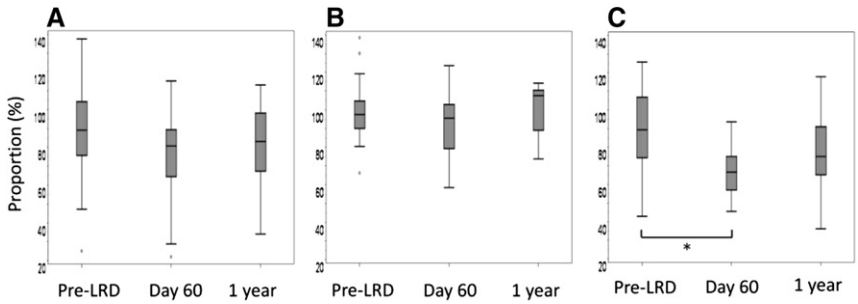

Figure 3. Percentages of FEV1 (A), TLC (B), and DL_{CO} (C) predicted for each value are shown at the time point of pre-LRD, day 60, and 1 year after RSV LRD. *P* for 3 parameters in %FEV1, %TLC, and %DLco are .249, .260, and .001, respectively. *$P < .05$, by Wilcoxon rank sum test.

even when a fully funded multicenter protocol was available (clinicaltrials.gov NCT00014391). Although this is the only outcome study of RSV LRD that has performed multivariable modeling, the statistical power to detect or rule out the possibility of smaller effects of antibody-based treatments such as palivizumab was limited. Based on post hoc calculations, the minimum detectable effect size in our study for antibody-based treatments would have been a 50% reduction of mortality. Thus, very large multicenter retrospective studies are needed to evaluate an effect size of $<10\%$ as suggested by our multivariable models. Whether such a relatively small effect would be deemed clinically significant is unclear given the enormous cost of the treatment (approximately U.S.$32,000 per 75 kg body weight for drug acquisition).

Our study also included only a small number of CBT recipients, which might represent a distinct clinical subgroup [11]. We analyzed CBT and BMT recipients together in this study because both groups have comparatively late immune reconstitution. However, the impact of CB is still unclear and requires larger numbers of patients. The exclusion of CBT recipients from the major analyses did not change the key conclusions of this article. Another limitation is that the cases occurred over 2 decades, which may have led to differences in supportive care practices and the timing of bronchoscopic evaluation. We accounted for this by including the year of transplantation and the degree of lung injury in our models.

In conclusion, our study identified 2 significant factors that are associated with improved outcome of RSV LRD in HCT recipients: the use of PBSC as the graft source and the lack of oxygen requirement at the time of diagnosis of LRD. Patients who had both factors at the time of diagnosis at RSV LRD had very favorable outcomes with aerosolized ribavirin treatment, which was administered to all patients (Figures 1C-F). These data could explain differences in outcome data reported over time and from different centers around the world. They could also serve as adjustment factors in multivariable models in future outcome analyses or to stratify patients in future randomized treatment trials.

Antibody therapies had no apparent effect on these associations, but our sample size prevented us from ruling out possible small effects. Multicenter studies are needed to validate these findings. Overall, our data suggest that the observed improvement in outcome of RSV disease in recent years is likely due to increased use of PBSC as graft source and the associated improved immune reconstitution, and to the increased early initiation of antiviral treatment before the onset of lung injury.

ACKNOWLEDGMENTS

We thank Deborah L. Reyes and Chris Davis for assisting with data collection and Margaret Green, MD, for suggestions regarding the analysis.

Financial disclosure: Partially supported by NIH grants CA18029, CA15704, HL081595, HL93294, K23HL091059, and L40AI071572. S.S. is a recipient of a fellowship from the Mochida Memorial Foundation for Medical and Pharmaceutical Research and the Joel Meyers Memorial Fund. A.P.C. also received support from the Seattle Children's Center for Clinical and Translational Research and CTSA grant ULI RR025014.

Conflict of Interest Statement: J.A.E. received research funding from Novartis and MedImmune. M.B. served as a consultant for Novartis and Gilead Sciences. J.W.C. is an employee of Gilead Sciences. All other authors declare no competing financial interests.

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