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Viral Infections (N Malavige, Section Editor)

Are We Overlooking the Use of Oral Ribavirin for Respiratory Syncytial Virus Infection Following Hematopoietic Stem Cell Transplantation?

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Abstract

Background Respiratory syncytial virus (RSV) is a common cause of respiratory infection following HSCT. We describe our experience using oral ribavirin (RBV) for RSV infections in HSCT recipients.

Methods Retrospective cohort analysis of HSCT recipients diagnosed with RSV infection and treated with either oral RBV or supportive care between September 2014 and April 2015.

Results Twenty-six HSCT recipients were identified as RSV-positive in this study. Oral RBV (mean daily dose 16.7 mg kg) was prescribed to 14 (54%) patients. A higher proportion of patients in the RBV group had lower respiratory tract infection (RTI) ($p = 0.007$) and were inpatient ($p < 0.001$) at diagnosis, with a higher proportion of acute graft-versus-host disease (GVHD) among patients with GVHD ($p = 0.06$), and more frequent prednisone ($p = 0.045$) or methylprednisolone use ($p = 0.008$). There was a higher frequency of oxygen requirement ($p = 0.035$) and longer hospital stays ($p < 0.001$) in the RBV group, but RSV-related mortality and progression from upper to lower RTI were not more frequent. Leukopenia and hemolysis were also not more frequent in the RBV group.

Conclusions Oral RBV appears to be well tolerated, but its benefit in RSV infections remains unclear. Randomized controlled trials are needed to further evaluate its safety and efficacy at escalating doses in this patient population.

Introduction

Respiratory syncytial virus (RSV) is one of the most common causes of respiratory viral infections in hematopoietic stem cell transplant (HSCT) recipients, with incidence ranging between 1 and 12% [1]. In contrast to the immunocompetent host, RSV infections in patients with HSCT are known to progress from self-limited upper respiratory tract infection (URTI) to severe, life-threatening lower respiratory tract infection (LRTI) in 18 to 55% of cases, with associated mortality as high as 80% if untreated [1–5]. The winter season represents the peak time for transmission, and nosocomial outbreaks are common. Clinical manifestations include nasal congestion, wheezing, and productive cough. RSV infection is associated with characteristic airflow decline, and hypoxia is common. Diffuse ground-glass infiltrates and bronchiolitis are characteristic radiologic findings. Risk factors for progression to LRTI include graft-versus-host disease (GVHD); infection in the pre-engraftment or early post-engraftment period (< 1 month); advanced age; lymphopenia; transplant from a mismatched, unrelated donor; myeloablative conditioning; and use of high-dose total body irradiation [6–11]. Guidelines from the Fourth European Conference on Infections in Leukemia (ECIL-4) suggest that oral or intravenous ribavirin (RBV) can be considered in patients with hematologic malignancy presenting with RSV respiratory disease; this recommendation lacks support from high-quality evidence [14]. RBV is a nucleoside analogue with broad-spectrum antiviral activity against RNA and DNA viruses. It is available in oral and aerosolized formulations in the USA and also in intravenous form in Europe. Aerosolized RBV is approved by the Food and Drug Administration (FDA) for the treatment of RSV-LRTI in hospitalized high-risk infants and children. Oral ribavirin is only FDA-approved for the treatment of hepatitis C virus infection in the adult population [12, 13].

A systematic review of the literature on RBV therapy showed that administration early in the course of RSV-related respiratory disease in HSCT recipients results in a reduced rate of progression to LRTI and lower RSV-related and all-cause mortality [4]. The majority of the studies included utilized aerosolized RBV. The use of aerosolized RBV is associated with multiple adverse events like bronchospasm, obstructive bronchiolitis, and nausea, as well as teratogenic effects on healthcare workers. It requires a special dispensing device to prevent healthcare worker exposure and is also difficult to administer in patients on

mechanical ventilation [5, 15–17]. Further, aerosolized RBV is also associated with a prohibitively high cost [18]. Oral RBV is a significantly inexpensive alternative and has been shown to be well tolerated in HSCT recipients, with mild hemolytic anemia as a common side effect that is typically reversible [5, 19, 20]. Thus, a growing number of medical centers, including ours, have adopted the use of oral RBV rather than aerosolized RBV [21, 22]. Herein, we describe a single institution experience with the use of oral RBV during an outbreak of RSV in HSCT recipients.

Methods

After obtaining permission from the Virginia Commonwealth University (VCU) Institutional Review Board, we conducted a retrospective analysis of all adult HSCT recipients diagnosed with RSV infection between September 2014 and April 2015 at the VCU Bone Marrow Transplant Program. Patients were included if they tested positive for RSV by multiplex polymerase chain reaction (PCR) performed on samples obtained by nasopharyngeal swab. Universal Transport Medium (UTM)™ kits were utilized for sample collection, and samples were delivered to the VCU microbiology laboratory on ice within 2 h of collection or stored refrigerated at 2 °C to 8° prior to delivery if acquired at a remote clinical area. PCR was performed using Cepheid's Xpert® Xpress Flu/RSV test reagent kit. The decision to test for RSV was at the discretion of the treating physicians.

Chart review was done to retrieve data on demographic and clinical baseline characteristics, presenting symptoms, radiographic findings, laboratory values, microbiology data, and clinical outcomes during the course of RSV infection, namely progression from URTI to LRTI, use of RBV, symptom resolution at 30 days, adverse events, duration of hospitalization, concomitant infections, and mortality. URTI was defined as RSV positivity in the presence of respiratory symptoms without new chest imaging findings. LRTI was defined as RSV positivity in the presence of both respiratory symptoms and new chest imaging findings, need for oxygen supplementation, presence of respiratory distress, or need for mechanical ventilation. Respiratory symptoms were defined as cough, nasal congestion, or sinus congestion. Overall and RSV-related mortality were assessed at 30 and 180 days following diagnosis of RSV infection. Adverse events of interest were hemolysis, anemia, and leukopenia during the course of RSV infection. Laboratory markers of hemolysis collected were hyperbilirubinemia, elevated serum lactate dehydrogenase (LDH), and presence of schistocytes on peripheral blood smear.

Data analysis was performed using GraphPad software. *P* values were calculated using Fisher's exact test for categorical variables and *t* test for continuous variables. *P* values less than 0.05 are considered statistically significant.

Results

During the study period, 26 HSCT recipients tested positive for RSV. Oral RBV was administered at the discretion of the treating physician based on the risk of progression or suspected LRTI. Fourteen (54%) patients received oral RBV (RBV group) and 12 (46%) patients received only supportive measures (supportive group). Sixteen (62%) patients were admitted to the hospital. Among those, 13 (81.3%) were already inpatient at the time of diagnosis, while 3 (18.8%) patients were admitted upon diagnosis. The median time from diagnosis to initiation of

RBV therapy was 26 days. The median duration of RBV therapy was 10 days, and the mean daily dose was 16.7 mg/kg/day.

Table 1. Baseline characteristics

	Oral RBV (*n* = 14), *n* (%)	No RBV (*n* = 12), *n* (%)	*p* value
Mean age (range)	47 (26–68)	59 (54–68)	*0.017*
Male	10 (71.4%)	7 (58.3%)	0.6
Indication for transplant			
ALL	3 (21.4%)	1 (8.3%)	0.59
AML	1 (7.1%)	3 (25%)	0.30
African-American	4 (21.6%)	0 (0%)	0.1
Allogenic BMT	12 (85.7%)	11 (91.7%)	1.0
Persistent relapsed disease	5 (35.7%)	4 (33.3%)	1.0
Myeloablative CR at BMT	7 (50.0%)	5 (41.7%)	0.71
Prednisone use[1]			
Average dose (mg/day)	33	21	*0.04*
Average duration (days)	5	14	0.33
Methylprednisolone[1]			
Average dose (mg/day)	61	0	*0.008*
Average duration (days)	14	0	*0.035*
Any GVHD[2]	6 (42.9%)	6 (50%)	1.0
Proportion acute GVHD	6/6 (100%)	2/6 (33.3%)	0.06
Location of GVHD			
Gastrointestinal tract	3/6 (50%)	No data	
Skin	2/6 (33.3%)	2/6 (33.3%)	1.0
Lung	1/6 (16.7%)	No data	
ISI score			
High-risk	6 (42.8%)	0 (0%)	*0.017*
Medium-risk	7 (50%)	11 (91.7%)	*0.035*
Low-risk	1 (7.2%)	1 (8.3%)	1.0
Inpatient	13[3] (93%)	3 (25%)	*< 0.001*
Intravenous immunoglobulin use during RSV	13 (93%)	2 (16%)	*< 0.001*
Immunosuppression/chemotherapy during RSV disease[4]	14 (100%)	9 (75%)	*0.008*
Mean WBC (10e9/L)[5]	2.86	7.03	*0.004*
Mean Hgb (gm/dL)[5]	9.1	10.2	0.07
Mean serum creatinine (mg/dL)[5]	0.88	1.24	0.07
Mean serum ALT (U/L)[5]	67.14	26.00	0.20
Mean total bilirubin (mg/dL)[5]	1.11	0.30	*0.02*

ALL acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *BMT* bone marrow transplant, *RSV* respiratory syncytial virus, *CR* conditioning regimen, *GVHD* graft-versus-host disease, *SCT* stem cell transplant, *HSCT* hematopoietic stem cell transplantation, *ISI* immunodeficiency scoring index Italics denoted statistically significant

[1]Use of prednisone or methylprednisolone after RSV diagnosis

[2]Three months prior to, during, or after RSV episode

[3]One patient was admitted 10 days after diagnosis with RSV

[4]Exposure to antithymoglobulin, busulfan, cyclophosphamide, total body irradiation, fludarabine, etoposide, photopheresis, carboplatin, or melphalan

[5]Biochemical parameters at time of RSV diagnosis

Baseline characteristics

Table 1 summarizes the baseline characteristics of the patients. Patients who received RBV were younger. The mean age for the RBV group was 47 (range 26–68) years vs 59 (range 54–68) years for the supportive group ($p = 0.017$). There was no difference in gender, race, indication for transplant, type of transplant, and use of myeloablative conditioning regimen. In terms of biochemical markers, there was no difference in baseline serum creatinine and alanine aminotransferase (ALT) levels among the groups; however, mean baseline total bilirubin was higher in the RBV group compared to supportive group (1.11 vs 0.30, respectively, $p = 0.02$). Acute GVHD was more common in the RBV group than in the supportive group, but this was not statistically significant. Steroid use was significantly higher in the RBV group, with a higher daily dose of prednisone ($p = 0.05$), as well as higher daily dose and duration use of methylprednisolone ($p = 0.008$ and $p = 0.035$, respectively). When classified according to the immunodeficiency scoring index (ISI) developed by Shah et al. [28] to predict progression to LRTI and RSV-related mortality in this patient population, six (42.8%) patients in the RBV group fell in the high-risk category vs none in the supportive group ($p = 0.017$). In contrast, 7 (50%) patients receiving RBV were classified as moderate-risk compared to 11 (91.7%) patients in the supportive group ($p = 0.035$). Most of the RBV group individuals required inpatient management compared to supportive group (93% vs 25%, respectively, $p < 0.001$). Intravenous immunoglobulin was used more often in the RBV group (93% vs 16%, respectively, $p < 0.001$).

Table 2. Clinical presentation

	Oral RBV ($n = 14$), n (%)	No RBV ($n = 12$), n (%)	p value
Mean number of days from HSCT to RSV positivity (range)	63 (0–578)	848 (16–3500)	*0.02*
LRTI due to RSV at diagnosis	10 (71.4%)	2 (16.7%)	*0.007*
Bronchiolitis	5	2	0.39
Pneumonitis	5	0	*0.04*
Supplemental O_2 during RSV episode	7[1] (50%)	1[2] (0%)	*0.035*
Concomitant infections			
Fungal PNA	4 (28.6%)	0 (0%)	0.10
Bacterial PNA	1 (7.1%)	0 (0%)	1.0
AFB PNA	0 (0%)	0 (0%)	1.0
Symptoms			
Cough	13 (93%)	12 (100%)	1.0
Nasal/sinus congestion	9 (64%)	8 (67%)	1.0
Rhinorrhea	1 (7%)	2 (17%)	0.58
Fever[3]	2 (14%)	0 (0%)	0.48

LRTI lower respiratory tract infection, *RSV* respiratory syncytial virus, *PNA* pneumonia, *AFB* acid-fast bacilli, *CMV* cytomegalovirus, *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *Hgb* hemoglobin Italics denoted statistically significant

[1]One of these seven patients required supplemental O_2 at time of RSV diagnosis; the rest developed this requirement later during RSV episode

[2]This patient required supplemental O_2 at time of RSV diagnosis

[3]Temperature equal to or greater than 38.3 °C

Clinical presentation

The mean time from transplant to RSV diagnosis was significantly longer in the RBV than the supportive group (63 days and 848 days, respectively, $p = 0.02$). LRTI due to RSV infection was significantly more common in the RBV group (71.4% vs 16.7%, $p = 0.007$). One patient in each group had a new supplemental O2 requirement at the time of diagnosis, but none of the patients in the supportive group developed a new O2 requirement during the course of RSV disease while 50% of those in the RBV group did (Table 2).

Clinical outcomes

Patients in the RBV group had longer hospital stays (20 days vs 1 day, $p < 0.001$). There was no statistically significant difference in the progression from URTI to LRTI, ICU admission, use of mechanical ventilation, overall and RSV-related mortality, and symptom resolution on day 30 did not differ among the groups (Table 3). There were three deaths in the RBV group: one due to disseminated mucormycosis (at 4 months post RSV diagnosis), one due to acute GVHD of the gut (at 15 days), and one due to sepsis (at 4 months). One patient in the

Table 3. Clinical outcomes

	Oral RBV ($n = 14$), n (%)	No RBV ($n = 12$), n (%)	p value
Mean duration of hospitalization (days)	19.7	1.17	*< 0.001*
Mean duration of RSV positivity (days)	40.25	32.5	0.6
Proportion of patients with URTI who progressed to LRTI[1]	0/4 (0%)	0/10 (0%)	1.0
New O_2 requirement during RSV episode	6[2] (43%)	0 (0%)	*0.02*
ICU admission during RSV episode	2[2] (14.3%)	0 (0%)	0.49
Mechanical ventilation use	1[2] (7.1%)	0 (0%)	1.0
30-day mortality	1[3] (7.1%)	0 (0%)	1.0
6-month mortality	2[4] (14%)	1[5] (8%)	1.0
RSV-related mortality at 6 months	0 (0%)	0 (0%)	1.0
Symptom resolution at day 30	11 (78.6%)	10 (83.3%)	1.0

[1]Progression from URTI to LRTI was defined as developing a new O_2 requirement, admission to the ICU, or need for mechanical ventilation during RSV course in a patient with URTI at time of diagnosis
[2]All these patients had LRTI at RSV diagnosis, hence not meeting the definition of progression from URTI to LRTI after RBV. The two patients who required ICU admission, one of which required mechanical ventilation, are included among the six patients who had a new O_2 requirement during RSV episode
[3]Fifteen days
[4]Four and 6 months
[5]Five months
Italics denoted statistically significant RSV respiratory syncytial virus, *ICU* intensive care unit, *O_2* oxygen

supportive group died of sepsis at 5 months. There were no deaths attributed to RSV.

Adverse events

The mean WBC at RSV diagnosis was 2.86 in the RBV group vs 7.03 (× 10e9/L) in the supportive group ($p = 0.004$); mean Hgb was 9.1 and 10.2 g/dL respectively ($p = 0.07$). There was no difference between the two groups with regard to mean change in white blood cell count. There was a significant decline in hemoglobin levels in the RBV group ($p = 0.03$), with 13 (93%) patients in this group requiring blood transfusions during the course of disease compared to 2 (17%) patients in the supportive group ($p < 0.001$) (Table 4). However, there was no difference in the number of patients who had laboratory abnormalities indicative of hemolysis, namely schistocytes on peripheral blood smear, and elevated lactate dehydrogenase level. There was also no difference in mean change in serum creatinine, ALT, and total bilirubin between the two groups (Table 4).

Table 4. Adverse events

	Oral RBV ($n = 14$), n (%)	No RBV ($n = 12$), n (%)	p value
Mean changes in WBC (range)	2.75 (3.33–6.08)	1.02 (6.00–7.03)	0.46
Mean changes in Hgb (range)	– 1.66 (0, – 3.3)	– 0.51 (0, – 2.1)	*0.03*
Mean change in serum creatinine	0.05	0.03	0.90
Mean change in serum ALT	42.29	2.50	0.50
Mean change in total bilirubin	1.10	0.01	0.35
Frequency of peripheral smear findings consistent with hemolysis	9 (61.5%)	4 (33.3%)	0.49
Frequency of LDH abnormality	8 (61.5%)	7 (70%)	1.0
Frequency of > 2 g drop of Hgb during RBV tx/RSV	5 (35.7%)	1 (8.3%)	0.36
Frequency of blood transfusion(s)	13 (92.9%)	2 (16.7%)	*< 0.001*

[1]More than twofold increase in total bilirubin during RSV disease course
[2]Presence of schistocytes on peripheral smear
[3]LDH level more than 250 units/L.
WBC white blood cell, *Hgb* hemoglobin, *LDH* lactate dehydrogenase, *RBV* ribavirin, *tx* treatment, *RSV* respiratory syncytial virus Italics denoted statistically significant

Discussion

In this retrospective cohort analysis of HSCT recipients with RSV, patients who received oral RBV were sicker at baseline and at higher risk for poor clinical outcomes than those who did not, yet they did not experience worse clinical outcomes in terms of progression from URTI to LRTI or RSV-related mortality, suggesting a potential protective effect of oral RBV. Oral RBV therapy was also well tolerated.

Patients treated with oral RBV more frequently had acute GVHD, which is known to be a risk factor for progression from URTI to LRTI, yet the frequency of progression from URTI to LRTI in this group was not higher [9]. The higher frequency of new or increasing oxygen requirements in the RBV group did not represent more progression from URTI to LRTI since these patients already had LRTI at diagnosis. Although patients who received RBV had more LRTI, O2 requirement, and longer hospital stays, they did not experience higher RSV-related mortality than the supportive care group, most of whom only had URTI at diagnosis. This may suggest a potential beneficial role of oral RBV in the treatment of RSV LRTI. Data from previous studies have suggested dose escalation of RBV to as high as 60 mg/kg/day [19, 29]. In our study, the mean dose of RBV was 16.7 mg/kg/day. It is possible that we could have seen an increased benefit with a higher dose, but we would have seen a higher rate of adverse events. In our cohort, oral RBV was well-tolerated with no increase in the occurrence of hemolysis, leukopenia, renal dysfunction, or hepatic derangement. Although we did observe a higher frequency of transfusion-requiring anemia in the group treated with RBV, this transfusion burden is expected to be reduced with current transfusion guidelines dictating a more restrictive hemoglobin threshold of 7 g/dL for hemodynamically stable medical patients compared to 8 g/dL at the time of this study [27].

RSV disease, and RSV-LRTI in particular, is known to be a strong predictor of mortality in HSCT recipients [5, 6, 18]. A systematic review has shown that ribavirin therapy, administered at the LRTI stage in any formulation, is associated with lower RSV-related mortality [5]. This systematic review also showed that RBV therapy at the URTI stage is associated with lower progression to LRTI. Although most of the studies included in this systematic review used aerosolized RBV, there is some data supporting the use of oral RBV in HSCT recipients. Consistent with our findings, there were no RSV-related deaths in a retrospective analysis of 34 moderately to severely immunocompromised patients treated with oral RBV, including HSCT recipients [22]. There was progression to neither LRTI nor RSV-related mortality observed in a case series of five HSCT recipients who received oral RBV [23]. In an analysis of 56 patients on a hematology and transplant unit, of which 40 (71%) had RSV-LRTI, treatment with oral RBV was found to be protective against mortality; moreover, there were no adverse events requiring medical intervention or dose reduction [24]. In another retrospective analysis whereby 23 HSCT recipients were treated with oral RBV, only 1 RSV-related death was observed, and treatment was well-tolerated with only minor adverse events [25]. In the only comparative study of oral versus aerosolized RBV in adult immunocompromised patients including 16 HSCT recipients, there was no significant difference in the progression from URTI to LRTI, 30-day mortality, and adverse effects [26]. The cost avoided by using oral instead of aerosolized RBV over a 1-year period was $1.2 million [26]. Our results add to the growing evidence suggesting that oral RBV is well-tolerated in HSCT recipients and hence may serve as a suitable, safe, and cost-effective alternative to the aerosolized form of RBV with potentially similar positive outcomes, namely lower RSV-related mortality and progression from URTI to LRTI.

Our study, similar to prior studies, has several notable limitations. First, the retrospective nature of the study, the non-standardized approach to

testing and treatment, and the small sample size limit the ability to draw conclusions in regard to causality. Second, patients treated with oral ribavirin were more likely to receive concomitant treatment with IVIG, which could have played a role in improving outcomes in this group as suggested in previous studies [5]. Third, the majority of our patient population had risk factors and baseline characteristics that put them in the high- and moderate-risk groups as per the ISI scoring system. Hence, our results may not be applicable to patients in the low-risk categories.

The above limitations aside, one can conclude that oral RBV was mostly well-tolerated and safe in our study. The use oral RBV in HSCT recipients remains a subject of controversy as its solid benefit in this patient population is yet to be elucidated. A randomized-controlled trial is worthwhile and needed to investigate the efficacy and safety of increasing oral RBV doses as an alternative to aerosolized RBV for the treatment of RSV respiratory disease in HSCT recipients.

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Compliance with Ethical Standards

Conflict of Interest

Mariam Assi declares that she has no conflict of interest. Brittany Cornfield declares that she has no conflict of interest. Dominic Engracia declares that he has no conflict of interest. Harold Chung declares that he has no conflict of interest. William Clark declares that he has no conflict of interest. John McCarty declares that he has no conflict of interest. Fernanda P. Silveira declares that she has no conflict of interest. Catherine Roberts declares that she has no conflict of interest. Amir Toor declares that he has no conflict of interest. Oveimar De la Cruz declares that has no conflict of interst.

Human and Animal rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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