J Pediatr Rev. 2014;2(2):66-71

JPR

Journal of Pediatrics Review

Mazandaran University of Medical Sciences

Use of Ribavirin treatment in Pre-transplant patients with Respiratory Syncytial Virus Upper Respiratory Tract Infection: Case report and Review of Literature

Ameneh Khatami[1*]

[1]Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, New South Wales, Australia

ARTICLE INFO

Article type:
Case report and Review of Literature

Article history:
Received: 1 Jul 2014
Revised: 2 Aug 2014
Accepted: 10 Aug 2014

Keywords:
Respiratory syncytial virus, Ribavirin, Immunosuppression, Paediatric, Bone marrow transplant

http://jpr.mazums.ac.ir

ABSTRACT

Respiratory syncytial virus infection in patients undergoing haematopoetic stem cell transplantation can be associated with high morbidity and mortality. Lymphocytopenia is an important factor associated with progression of upper to lower respiratory tract infection. The only licensed antiviral treatment for Respiratory syncytial virus available currently is ribavirin, although additional immunomodulatory therapies may also play a beneficial role. We report two cases of pre-transplant patients with acute myeloid leukaemia who were considered for ribavirin treatment for Respiratory syncytial virus upper respiratory tract infection and review the published literature on this. The use of ribavirin in immunocompromised patients with Respiratory syncytial virus upper respiratory tract infection to reduce the risk of progression to lower respiratory tract infection is unclear. In patients with Respiratory syncytial virus upper respiratory tract infection detected in the pre-transplant stage, delay of transplantation remains the most effective method of reducing morbidity and mortality.

Introduction

Respiratory syncytial virus (RSV) infection in immunocompromised patients, especially those with defects in cell mediated immunity is associated with high morbidity and mortality. Lymphocytopenia is an important factor associated with progression of upper to lower respiratory tract infection (LRTI).[1] The only licensed antiviral treatment for RSV available currently is ribavirin. The use of ribavirin in immunocompromised patients with LRTI has some evidence for efficacy in reducing mortality.[2 3] The use of ribavirin in

***Corresponding Author:** *Ameneh Khatami, MD, Fellow in Infectious Diseases & Microbiology, Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, NSW, Australia*
Mailing Address: Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, LMB 4001, Westmead NSW 2145, Australia
Tel: +612 98453274
Fax: + 612 98453291
Email: ameneh.khatami@health.nsw.gov.au

these patients with upper respiratory tract infections (URTI) to reduce the risk of progression to lower respiratory tract infection (LRTI) is less well defined. We report two cases of pre-transplant paediatric patients with acute myeloid leukaemia who were considered for ribavirin treatment for RSV URTI and review the published literature on this.

Case 1

An 8 year-old girl with relapsed acute myeloid leukaemia (AML), scheduled for an allogenic stem cell transplant in six weeks was admitted for routine chemotherapy (fludarabine and high-dose cytarabine) with symptoms of an upper respiratory tract infection (URTI) including cough from three days prior to admission. AML relapse had been diagnosed two months prior based on results from a bone marrow aspirate. *Respiratory syncytial virus* (RSV)-A was detected by polymerase chain reaction (PCR) on a nasopharyngeal aspirate (NPA). No other respiratory viruses were detected by PCR including negative tests for *Influenza* A and B, *Rhinovirus*, *Enterovirus*, *Adenovirus*, *Human metapneumovirus*, *Parainfluenza* virus types 1-4, *Coronavirus* and *Bocavirus*. She did not have any clinical signs or symptoms of a lower respiratory tract infection (LRTI): not any respiratory distress, did not require supplemental oxygen and had no clinical signs of pneumonitis. A chest X-ray was not performed. On day five of admission, she was started on nebulised ribavirin treatment 2g every eight hours. Her initial lymphocyte count was 0.8 x 10^9/L and dropped to 0 x 10^9/L by day six of admission. She became neutropenic (neutrophil count <0.5 x 10^9/L) on day 10 of admission. After 10 days of ribavirin treatment, advice was sought from the infectious disease (ID) team on the duration of treatment. Repeat NPA testing one week after the initial test had been negative for all respiratory viruses by PCR. Advice was given to stop ribavirin treatment given that the patient was afebrile, had no symptoms or signs of LRTI and had a negative NPA. The bone marrow transplant (BMT) team wanted to continue nebulised ribavirin until the patient had two negative NPA's at least one week apart and had a lymphocyte count greater than 0.5 x 10^9/L and so treatment was continued.

On day 16 of admission the patient developed a fever which persisted for four days. A veridans group *Streptococcus* species was identified from one lumen of a double-lumen central venous device. The patient had no detectable neutrophils in her peripheral blood at the time and so she was treated empirically with broad spectrum intravenous (IV) antibiotics: piperacillin-tazobactam and vancomycin for seven days, gentamicin for two days. Seven sets of subsequent blood cultures were all negative. Nebulised ribavirin was stopped after 17 days treatment due to a shortage of supply in the hospital. At that point her neutrophil count had increased to over 0.5 x 10^9/L; however her lymphocyte count was still only 0.2 x 10^9/L. Although ribavirin was again available in the hospital after a day, the ID team advised that the patient should remain off ribavirin treatment as she was asymptomatic, and to undertake weekly surveillance NPA's to be performed until the date of her transplant. She was discharged home after 25 days in hospital and had three negative NPA samples during her admission.

Case 2

A 15 month-old boy with recent central nervous system relapse of AML was admitted for febrile neutropenia following high dose cytarabine and fludarabine chemotherapy. AML relapsed had been diagnosed two

weeks prior based on results from cerebrospinal fluid. He was treated empirically with broad spectrum IV antibiotics: piperacillin-tazobactam and vancomycin for seven days, gentamicin for four days. He was awaiting allogenic stem cell transplant in approximately four weeks. He had symptoms of an upper respiratory virus infection (URTI) and RSV-A and *Rhinovirus* were detected on an NPA by PCR. No other respiratory viruses were detected by PCR including negative tests for *Influenza* A and B, *Enterovirus*, *Adenovirus*, *Human metapneumovirus*, *Parainfluenza virus* types 1-4, *Coronavirus* and *Bocavirus*. He did not have any clinical signs or symptoms of a LRTI: he did not have any respiratory distress, did not require supplemental oxygen and did not have clinical signs of pneumonitis. A chest Xray was not performed. His fevers resolved after four days. His lymphocyte count was 0.6 x 10^9/L on admission and increased to >1.0 x 10^9/L within four days; however he remained neutropenic with no detectable neutrophils in the peripheral blood. On day four of admission, the BMT team wanted to start nebulised ribavirin for two weeks; however given that he was afebrile at that stage, his lymphocyte count was greater than 1.0 x 10^9/L and he did not have clinical evidence of a LRTI, the ID team advised against treatment. A repeat NPA sample on day five was negative for RSV and only positive for *Rhinovirus* by PCR. Multiple blood cultures remained negative and so IV antibiotics were ceased and he was discharged home after eight days with a neutrophil count of 0.3 x 10^9/L.

Discussion

Assessing risk in patients with RSV URTI

RSV is a cause of serious respiratory infections in paediatric patients and can be especially devastating in paediatric haematopoiec stem cell transplant (HSCT) recipients. RSV pneumonia or pneumonitis occurring in HSCT recipients or patients with acute leukaemia carries a high mortality risk.[4-8] Furthermore, immunocompromised patients with URTI have a moderate risk of developing LRTI.[6] In a recent reasonably large retrospective series of laboratory-confirmed RSV infections in allogenic HSCT recipients (n = 280), risk factors identified in multivariate analyses to be associated with RSV LRTI (n = 80) and all-cause mortality (n = 44), included age, male sex, neutropenia and lymphocytopenia.[9] Lymphocytopenia has been shown in several studies, to be associated with risk of progression of RSV URTI to LRTI.[1 8-10] In the most recent report by Kim *et al* of 181 HSCT patients, which included a small number of paediatric patients, lymphocyte count <0.1 × 10^9/L at the time of RSV infection was found to be an independent risk factor for progression to LRTI, whereas an absolute lymphocyte count of >1.0 × 10^9/L was completely protective against progression to LRTI.[1] In the first case described above, the patient had an absolute lymphocytopenia on admission and her lymphocyte count was slow to recover. Based on evidence from the data available to date, this placed her at an increased risk of progressing to RSV LRTI. The second patient had a lymphocyte count of 0.6 x 10^9/L on admission and this increased to greater than 1.0 x10^9/L within a few days. For this patient we would expect a low risk of progression to RSV LRTI.

Treatment of RSV URTI in transplant recipients

The only licensed antiviral treatment for RSV available currently is ribavirin, a guanosine

analogue with broad spectrum *in vitro* and *in vivo* activity against RNA and DNA viruses. It is traditionally administered as a small particle aerosol to immunocompromised patients with RSV LRTI. Its efficacy remains controversial due to the lack of data based on well-designed controlled trials. In addition, aerosolised drug administration is limited by potential toxicity (bronchoconstriction, increased cough and nausea) and possible teratogenic exposure of caregivers and nurses and the need for special air-flow and room conditions. Intravenous administration of ribavirin can avoid these disadvantages, but its efficacy and safety are not well established, especially in the paediatric HSCT setting. The most common adverse effect from systemic administration appears to be mild reversible, anaemia, due to haemolysis.

Several small cases series in immunocompromised patients have suggested that early therapy with ribavirin (with or without additional RSV-specific or pooled immunoglobulin) for RSV URTI, may prevent spread of the virus to the lower respiratory tract, and may prevent the progression of LRTI to severe pneumonitis with fatal outcome.[2 3 11-13] In the series of laboratory-confirmed RSV infections in allogenic HSCT recipients described above a further risk factor identified in multivariate analyses to be associated with RSV LRTI and all-cause mortality was lack of ribavirin-based antiviral therapy at the URTI stage.[9] In this study, aerosolised ribavirin-based therapy at the URTI stage was the single most significant factor in reducing the risk of RSV LRTI (83%), all-cause mortality (57%) and RSV-associated mortality (87%) in these patients.

In a recent review of studies conducted in adult HSCT patients it was demonstrated that regardless of therapy, almost 50% of patients with RSV URTI progressed to RSV LRTI and around 30-50% of patients with RSV LRTI had RSV-related or attributable mortality, especially when contracted in the first few months after transplantation.[14] For patients with URTI treated with ribavirin, regardless of the form or duration of therapy, the rate of progression to LRTI was much lower than in patients who did not receive any form of RSV therapy; and the mortality rate, was lower in patients who were treated at the LRTI stage. Interestingly, patients who received aerosolized ribavirin alone had worse outcomes than patients that received any additional immunoglobulin therapy. The studies included in this review are however mostly limited by their retrospective nature, small sample sizes, heterogeneous treatment regimens and uncontrolled designs. The only existing controlled trial of aerosolised ribavirin in HSCT recipients was only able to recruit 14 patients and failed to demonstrate a difference in outcomes despite a trend for lower viral loads in the ribavirin treated patients.[15] Furthermore, generalisation of these data to paediatric patients is problematic and data specifically from the paediatric setting are even more scant.

In paediatric HSCT patients identified as RSV-positive in upper respiratory tract samples who were asymptomatic at the time, RSV infection cleared after one or two 5-day treatment courses of aerosolised ribavirin. None of these patients developed symptoms of upper or lower respiratory tract disease[16 17]; however it is not clear that such preventative treatment of asymptomatic patients with ribavirin is necessary to prevent clinically significant disease. In a series of 336 allogeneic transplants performed at the BMT unit in Bristol, of which the majority were in paediatric patients, there were five deaths (19.2%) directly attributable to RSV infection (n = 26) and one death due to an

intracranial haemorrhage during an RSV infection.[7] All of the deaths occurred in patients with LRTI. In a further small proportion of cases, RSV infection may have contributed to graft failure. The only major factor affecting outcome was the presence of clinically diagnosed LRTI. Unrelated donor transplant recipients tended to do worse, as did those with AML as the underlying disease. Aerosolised, intravenous or combination ribavirin treatment did not significantly affect outcome of infection; although in this study efficacy may have been reduced by a delay between development of symptoms and start of treatment (median delay of one week).

Treatment of RSV URTI in pre-transplant patients

In patients with pre-transplantation RSV URTI, delay of HSCT was associated with a lower risk of pneumonia than when there was no delay (1/34 patients compared to 2/3 patients respectively).[18] Treatment of a small number of patients with ribavirin at the URTI stage did not reduce rates of progression to pneumonia. The post-transplantation RSV infection rate of 6.5% in this series did not appear to be higher than the rate seen in patients who underwent transplantation without pre-transplantation RSV infection. Furthermore, no apparent difference in the survival rate of patients with pre-transplant RSV infection was seen when compared with patients without RSV infection, suggesting that if transplantation is delayed before the start of conditioning, pre-transplant RSV infection does not result in increased mortality or risk of post-transplant RSV infection. This finding is relevant to the two cases described above where RSV URTI occurred, and had clinically resolved, long before conditioning for HSCT was to be initiated.

Conclusion

The two cases described above highlight the anxiety associated with identification of RSV URTI in pre-HSCT paediatric patients. Such infections invariably lead to delay in transplantation, however given that ribavirin treatment is very expensive and not without potential toxicity, and there is a lack of good evidence to suggest efficacy, it is unclear whether treatment with ribavirin is justified. Specific risk factors that should be taken into consideration when assessing patients include underlying diagnosis, time to transplantation, lymphocyte count at the time of upper respiratory tract infection and evidence of clinical LRTI. Randomised placebo-controlled trials of ribavirin treatment are greatly in need to guide clinical practice.

Conflict of Interest

None declared.

Funding/Support

None declared.

References

1. Kim YJ, Guthrie KA, Waghmare A, Walsh EE, Falsey AR, Kuypers J, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis 2014;209(8):1195-204.
2. Torres HA, Aguilera EA, Mattiuzzi GN, Cabanillas ME, Rohatgi N, Sepulveda CA, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. Haematologica 2007;92(9):1216-23.
3. Anak S, Atay D, Unuvar A, Garipardic M, Agaoglu L, Ozturk G, et al. Respiratory syncytial virus infection outbreak among pediatric patients with oncologic diseases and/or BMT. Pediatric pulmonology 2010;45(3):307-11.
4. 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(6):987-93.
5. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. Am J Med 1997;102(3A):10-8; discussion 25-6.
6. Bowden RA. Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. Am J Med 1997;102(3A):27-30; discussion 42-3.
7. McCarthy AJ, Kingman HM, Kelly C, Taylor GS, Caul EO, Grier D, et al. The outcome of 26 patients with respiratory syncytial virus infection following allogeneic stem cell transplantation. Bone Marrow Transplant 1999;24(12):1315-22.
8. 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 transplantation 2001;28(5):479-84.
9. Shah DP, Ghantoji SS, Shah JN, El Taoum KK, Jiang Y, Popat U, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. J Antimicrob Chemother 2013;68(8):1872-80.
10. Martino R, Porras RP, Rabella N, Williams JV, Ramila E, Margall N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2005;11(10):781-96.
11. Sparrelid E, Ljungman P, Ekelof-Andstrom E, Aschan J, Ringden O, Winiarski J, et al. Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections. Bone Marrow Transplant 1997;19(9):905-8.
12. McColl MD, Corser RB, Bremner J, Chopra R. Respiratory syncytial virus infection in adult BMT recipients: effective therapy with short duration nebulised ribavirin. Bone Marrow Transplant 1998;21(4):423-5.
13. Molinos-Quintana A, Perez-de Soto C, Gomez-Rosa M, Perez-Simon JA, Perez-Hurtado JM. Intravenous ribavirin for respiratory syncytial viral infections in pediatric hematopoietic SCT recipients. Bone Marrow Transplant 2013;48(2):265-8.
14. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. Blood 2011;117 (10):2755-63.
15. 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(2):245-9.
16. Adams R, Christenson J, Petersen F, Beatty P. Pre-emptive use of aerosolized ribavirin in the treatment of asymptomatic pediatric marrow transplant patients testing positive for RSV. Bone Marrow Transplant 1999;24(6):661-4.
17. Adams RH. Preemptive treatment of pediatric bone marrow transplant patients with asymptomatic respiratory syncytial virus infection with aerosolized ribavirin. Biol Blood Marrow Transplant 2001;7 Suppl:16S-18S.
18. Peck AJ, Corey L, Boeckh M. Pretransplantation respiratory syncytial virus infection: impact of a strategy to delay transplantation. Clin Infect Dis 2004;39(5):673-80.