



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

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ABSTRACT

Respiratory syncytial virus infection in patients undergoing haematopoietic 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

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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 $0.8 \times 10^9/L$ and dropped to $0 \times 10^9/L$ by day six of admission. She became neutropenic (neutrophil count $<0.5 \times 10^9/L$) 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 $0.5 \times 10^9/L$ 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 $0.5 \times 10^9/L$; however her lymphocyte count was still only $0.2 \times 10^9/L$. 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 $0.6 \times 10^9/L$ on admission and increased to $>1.0 \times 10^9/L$ 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 $1.0 \times 10^9/L$ 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 $0.3 \times 10^9/L$.

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 haematopoietic 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 $<0.1 \times 10^9/L$ at the time of RSV infection was found to be an independent risk factor for progression to LRTI, whereas an absolute lymphocyte count of $>1.0 \times 10^9/L$ 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 $0.6 \times 10^9/L$ on admission and this increased to greater than $1.0 \times 10^9/L$ 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 allogeneic 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 disease¹⁶¹⁷; 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.

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