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Article in *Pediatric Blood & Cancer* · June 2017

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Intravenous palivizumab in respiratory syncytial virus infection after hematopoietic stem cell transplant in children

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Grant sponsor: FONDECYT; Grant numbers: 1130911 and 11121536.

Abstract

Respiratory syncytial virus (RSV) infection can cause lower respiratory tract disease and mortality in pediatric hematopoietic stem cell transplant (HSCT) recipients. We report two children who underwent HSCT and developed RSV infection simultaneously at the Bone Marrow Transplant Unit. The treatment with intravenous palivizumab was provided and sequential viral loads were measured in nasopharyngeal (NP) and whole blood samples. To our knowledge, this is the first report where RSV loads were measured in parallel (NP and blood), before and after palivizumab, in correlation with a favorable clinical outcome in both cases.

KEYWORDS

children, hematopoietic stem cell transplant, palivizumab, respiratory syncytial virus

1 | INTRODUCTION

Respiratory syncytial virus (RSV) can be associated with severe respiratory tract infections in immunocompromised patients.¹ In pediatric hematopoietic stem cell transplant (HSCT) recipients, RSV infection presents a high risk of progression to the lower respiratory tract and increased mortality rates.²⁻⁴ Limited data suggest that detection of RSV-RNA in serum may be a marker of lung injury and poor outcome.³ Uncontrolled studies have shown that combined therapy with ribavirin and polyclonal or monoclonal antibodies is associated with decreased mortality,^{5,6} and a lower effect when monoclonal antibodies are administered alone.⁷ A report of two children with leukemia suggested that intravenous (IV) palivizumab, a monoclonal antibody against the RSV-F protein, may be a treatment option for persistent RSV infection.⁸ The impact of IV palivizumab on respiratory or systemic viral loads and clinical outcomes in immunocompromised children has not been defined.

We report two pediatric patients who underwent HSCT and developed RSV infection in the immediate and late posttransplant periods. After administration of IV palivizumab, sequential viral loads were measured in nasopharyngeal (NP) and whole blood samples. This report was approved by the Director of the Hospital and consented by the parents.

2 | CASE REPORTS

During winter of 2014, two patients who were profoundly immunosuppressed post-HSCT developed respiratory symptoms while hospitalized in the Bone Marrow Transplant Unit at Hospital Calvo Mackenna in Santiago, Chile. NP samples were tested by direct fluorescence assay (DFA) and quantitative PCR (qPCR), detecting RSV in both patients. RSV genomic loads were sequentially analyzed in NP and whole blood samples by qPCR on days 1, 3, 4, 5, 7, and 14. PCR assays were performed using LightMix® Kit RSV (TIB Molbiol, Berlin, Germany) with a sensitivity of 10 copies of DNA. Cycling conditions: 95°C for 10 min; and 50 cycles of 95°C for 5 sec, 62°C for 5 sec, and 72°C for 15 sec.

Abbreviations: ALC, absolute lymphocyte counts; CMV, cytomegalovirus; DFA, direct fluorescence assay; GvHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; IV, intravenous; LRTI, lower respiratory tract infection; MSD, matched sibling donor; NP, nasopharyngeal; qPCR, quantitative PCR; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection

Upper and lower respiratory tract symptoms, white blood cells, and absolute lymphocyte counts (ALC) were recorded daily. RSV genotype was also determined based on the methodology described by Peret et al.⁹

2.1 | Patient 1

A 13-year-old female with acute promyelocytic leukemia diagnosed in July 2012 was coursing a second relapse. HSCT with an human leukocyte antigens matched sibling donor (MSD) was programmed. Two weeks before admission, she presented symptoms of upper respiratory tract infection (URTI). RSV was detected by DFA, but the symptoms did not progress. She received a myeloablative conditioning regimen based on busulfan (16 mg/kg/total dose) on days -6 to -3 and cyclophosphamide (60 mg/kg/day) on days -2 and -1. Prophylaxis for graft versus host disease (GvHD): cyclosporine A (CsA) since day -1, for levels 200–250 ng/ml. Infection prophylaxis regimen was acyclovir, fluconazole, and weekly intravenous immunoglobulin.

The patient underwent an MSD HSCT on July 9, 2014 (total nucleated cells 1.38×10^8 /kg, mononuclear cells 0.51×10^8 /kg, CD 34 + 0.39×10^6 /kg). On day +4, she presented a febrile neutropenia episode starting meropenem (considering the isolation of *Klebsiella pneumoniae* extended spectrum beta lactamase (+) in urine culture) and linezolid. She completed 13 days of treatment. On day +11 after HSCT, while ALC was very low (ALC = 70), she presented URTI symptoms. RSV was identified by DFA and confirmed by qPCR. Genotyping revealed an RSV-B, Buenos Aires (BA) strain. Viral loads were determined sequentially (Table 1). RSV-RNA was detected in NP and blood samples. On day +13, she received IV palivizumab (15 mg/kg) as the only RSV-directed antiviral therapy. A significant decrease in viral loads in blood (3.4 log) and NP (2 log) within 24 hr of administration was observed, along with clinical resolution of respiratory symptoms. No progression to lower respiratory tract infection (LRTI) occurred, defined by no need for supplemental oxygen, normal lung auscultation, and a negative chest X-ray. She engrafted on day +19 and was discharged on day +23.

2.2 | Patient 2

A 12-year-old male was diagnosed in January 2012 with severe aplastic anemia. He underwent MSD HSCT in July 2012 with a conditioning regimen of cyclophosphamide 50 mg/kg/day for 4 days and total nodal irradiation (7 Gy). GvHD prophylaxis with CsA and methotrexate was received. He developed multiple post-HSCT complications: 10 episodes of cytomegalovirus (CMV) reactivations; CMV retinitis; acute GII–GIII cutaneous GvHD and severe cutaneous chronic GvHD, gut GvHD; severe adverse reactions to vancomycin, meropenem, albumin, immunoglobulin, and radiologic contrast; deep vein thrombosis; and multiple bacterial infections. Twenty-three months after transplantation—under infection prophylaxis with cotrimoxazole, fluconazole, and valganciclovir—he underwent intensification of the immunosuppressive therapy due to an extensive chronic GvHD, requiring weekly methotrexate and daily methylprednisolone

(1 mg/kg/day). After 1 month, and while hospitalized (July 20, 2014), he developed URTI symptoms that progressed to pneumonia within 48 hr, requiring supplemental oxygen administration. ALC was <1,500. Computerized tomography chest scan showed parenchyma involvement compatible with atypical pneumonia. NP samples were obtained and tested by DFA and qPCR, detecting RSV. Genotype analysis identified an RSV-A Ontario (ON) strain. RSV-RNA detection in blood was negative. He received IV palivizumab (15 mg/kg) 3 days after symptoms onset because of his severe immunocompromised status and fast progression to LRTI. Neither supportive therapy (intravenous immunoglobulin, antibiotics) nor RSV-directed antiviral therapy was indicated. NP RSV loads were quantified as shown in Table 1. Respiratory symptoms did not progress and supplemental oxygen was discontinued 7 days after palivizumab administration. Negative RSV detection by DFA was obtained 12 days after palivizumab treatment, although it remained positive by qPCR until discharge.

3 | DISCUSSION

We report two contemporary cases of RSV infection in children at high risk of severe respiratory infection in a Bone Marrow Transplant Unit. IV palivizumab was administered as a rescue therapy because of their high risk and with concerns of a nosocomial outbreak. To our knowledge, this is the first report where RSV loads were simultaneously measured in NP and blood samples, before and after the administration of palivizumab, and the first reported case of an immunocompromised patient with RSV infection without LRTI and detection of RSV-RNA in the blood.

Waghmare et al.³ described that RSV-RNA detection in plasma or serum was associated with poor clinical outcomes in HSCT patients. Interestingly, in our first patient, although high levels of viral loads were detected in NP and blood within the first few days of upper respiratory symptoms, they became undetectable by day 5 after palivizumab, with resolution of respiratory symptoms at day 4 and no progression to the lower respiratory tract. It is also remarkable that she had a recent RSV infection, and 12 days after transplant she started respiratory symptoms and high RSV loads. We suspected a viral reactivation rather than RSV reinfection.

In the second case, despite higher RSV loads in the upper respiratory tract, with a more severe infection (lower respiratory symptoms), no RSV-RNA was detected in the blood. Although a more robust immune response can be suspected, it is not possible to confirm, since no more immunologic data were achieved (IgG, IgA levels, peripheral blood immunophenotype). IV palivizumab was administered when lower respiratory symptoms were present. RSV loads in the nasopharynx—although significantly lower—remained positive at discharge, with a resolution of upper and lower respiratory symptoms, day 7 after RSV diagnosis.

Different RSV genotypes were detected, the novel RSV-A ON and the RSV-B BA, which helped to rule out a nosocomial transmission. The RSV-A ON has been identified in adult HSCT recipients during 2011–2013 season,¹⁰ with no significant differences in the severity of the disease compared to other RSV-A and RSV-B genotypes.

TABLE 1 Laboratory findings and clinical evolution of two children with respiratory syncytial virus infection after hematopoietic stem cell transplant

	Day 1 RSV DFA +	Day 3	Day 4	Day 5	Day 7	Day 14	RSV Genotype
Patient 1							
Nasopharyngeal PCR (RSV-RNA log ₁₀ copies/ml)	5.78	3.67	5.09	Negative	Negative	Negative	GB-BA
Blood PCR (RSV-RNA log ₁₀ copies/ml)	7.80	4.35	Negative	Negative	Negative	Negative	
Upper respiratory symptoms	(+)	(+)	(+)	(-)	(-)	(-)	
Lower respiratory symptoms	(-)	(-)	(-)	(-)	(-)	(-)	
WBC (x mm ³)/ALC	170/70	600/198	1,880/451	2,240/358	4,760/438	2,780/431	
Patient 2							
Nasopharyngeal PCR (RSV-RNA log ₁₀ copies/ml)	8.19	6.47	7.00	Not done	6.37	5.01	GA-ON
Blood PCR (RSV-RNA log ₁₀ copies/ml)	Negative	Negative	Negative	Not done	Negative	Negative	
Upper respiratory symptoms	(+)	(+)	(+)	(+)	(-)	(-)	
Lower respiratory symptoms	(+)	(+)	(+)	(+)	(+)	(-)	
WBC (x mm ³)/ALC	9,530/667	6,900/345	7,350/750	6,210/857	8,140/1042	7,340/881	

RSV, respiratory syncytial virus; DFA+, positive direct immunofluorescence assay; WBC, white blood cells; ALC, absolute lymphocyte count; GA-ON, group A, Ontario; GB-BA, group B, Buenos Aires.

While the treatment of RSV infection with palivizumab is controversial, it might be useful in patients at high risk for severe respiratory infection and the timing of administration may be a key factor to attain positive outcomes. As observed in our patients, and as previously reported in the animal model,¹¹ the sooner the anti-RSV monoclonal was administered in relation to the course of infection, the sooner the resolution of respiratory symptoms and viral loads were achieved. A recent report¹² conducted in adult patients with hematological malignancies and viral respiratory infections reported long-term viral shedding associated with HSCT and mainly in patients with RSV infection (median:80 days). Previous studies in the murine model showed that palivizumab decreased RSV replication in the respiratory tract when used as preexposure prophylaxis or as early therapy (−24, +1, or +48 hr from inoculation).¹³ Our study has limitations such as mainly derived from the small sample size. Nevertheless, we were able to simultaneously and sequentially characterize clinical and virologic factors during and up to 14 days from the RSV diagnosis.

Early administration of IV palivizumab might be useful in selected patients with severe immunosuppression. A combination of clinical, immune, and virologic biomarkers from nasal and systemic compartments may help to identify the subjects who will benefit from antiviral therapy. Further studies are required to define the utility and clinical benefit of treatment with monoclonal antibodies in immunocompromised patients.

ACKNOWLEDGMENTS

This study was supported by research funding from FONDECYT (grant numbers 1130911 and 11121536). The authors thank Mónica Peña for her valuable technical assistance and Julia Palma for her insightful advice.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352(17):1749–1759.
- Martino R, Porras RP, Rabella 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. *Biol Blood Marrow Transpl*. 2005;11(10):781–796.
- Waghmare A, Campbell AP, Xie H, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. *Clin Infect Dis*. 2013;57(12):1731–1741.
- Chu HY, Chin J, Pollard J, Zerr DM, Englund JA. Clinical outcomes in outpatient respiratory syncytial virus infection in immunocompromised children. *Influenza Other Respi Viruses*. 2016;10(3):205–210.
- Committee on Infectious Diseases. From the American Academy of Pediatrics: policy statements—modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):1694–1701.
- Chávez-Bueno S, Mejías A, Merryman RA, et al. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. *Pediatr Infect Dis J*. 2007;26(12):1089–1093.
- de Fontbrune FS, Robin M, Porcher R, et al. Palivizumab treatment of respiratory syncytial virus infection after allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis*. 2007;45(8):1019–1024.
- Santos RP, Chao J, Nepo AG, et al. The use of intravenous palivizumab for treatment of persistent RSV infection in children with leukemia. *Pediatrics*. 2012;130(6):e1695–e1699.
- Peret TC, Hall CB, Schnabel KC, Golub JA, Anderson LJ. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. *J Gen Virol*. 1998;79(Pt 9):2221–2229.
- Avadhanula V, Chemaly RF, Shah DP, et al. Infection with novel respiratory syncytial virus genotype Ontario (ON1) in adult hematopoietic cell transplant recipients, Texas, 2011–2013. *J Infect Dis*. 2015;211(4):582–589.
- Torres JP, Gomez AM, Khokhar S, et al. Respiratory syncytial virus (RSV) RNA loads in peripheral blood correlates with disease severity in mice. *Respir Res*. 2010;11(125):1–11.
- Lehners N, Tabatabai J, Prifert C, et al. Long-term shedding of influenza virus, parainfluenza virus, respiratory syncytial virus and nosocomial epidemiology in patients with hematological disorders. *PLoS One*. 2016;11(2):e0148258.
- Mejías A, Chávez-Bueno S, Ríos AM, et al. Anti-respiratory syncytial virus (RSV) neutralizing antibody decreases lung inflammation, airway obstruction, and airway hyperresponsiveness in a murine RSV model. *Antimicrob Agents Chemother*. 2004;48(5):1811–1822.

How to cite this article: Torres JP, Tapia LI, Catalán P, la Maza VD, Mejías A. Intravenous palivizumab in respiratory syncytial virus infection after hematopoietic stem cell transplant in children. *Pediatr Blood Cancer*. 2017;00:e26667. <https://doi.org/10.1002/pbc.26667>