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Effective use of oral ribavirin for respiratory syncytial viral infections in allogeneic haematopoietic stem cell transplant recipients

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SUMMARY

Background: Respiratory syncytial virus (RSV) is a frequent cause of respiratory viral infections, increasing the morbidity and mortality in allogeneic haematopoietic stem cell transplantation (HSCT) recipients. Little is known about the best management strategy in this immunocompromised group and there are very few data on oral ribavirin treatment.
Aim: To evaluate the effectiveness of oral ribavirin in allogeneic HSCT patients with RSV infection.
Methods: Twenty-three RSV cases treated with oral ribavirin were analysed retrospectively. RSV diagnosis was established by polymerase chain reaction assay. Oral ribavirin was initiated at 15 mg/kg/day in three divided doses for 10 days, with no subsequent dose escalation, as per centre policy.
Findings: At diagnosis, seven patients presented with lower respiratory tract infection (RTI), whereas 16 had upper RTI. Oral ribavirin was well tolerated with minor adverse effects. The median treatment duration was 10 days (range: 5–47). After a median follow-up of 17 months (range: 4–48), 17 patients are alive. We recorded one RSV-related and five non-related deaths.
Conclusion: To our knowledge, this is the largest single centre study yet performed on adult allogeneic HSCT recipients with RSV infection treated with oral ribavirin. Prompt initiation of treatment is essential and may avoid hospital admission. Our experience supports the use of oral ribavirin, but large prospective studies are needed to determine the optimal therapy in this patient group.

Introduction

Respiratory syncytial virus (RSV) is one of the most frequent causes of respiratory viral infections in patients undergoing haematopoietic stem cell transplantation (HSCT) and is

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associated with increased morbidity and mortality. RSV infections are predominant in the cold season and range from self-limiting upper respiratory tract infection (URTI) to lower respiratory infection (LRTI), especially in immunocompromised individuals.[1,2] Progression to LRTI may be observed in 38% (range: 0–68%) of leukaemia and HSCT patients, with an average mortality of 32% (range: 0–70%) as described previously.[3,4]

The most common symptoms are coryzal symptoms, i.e. fever, nasal congestion, sore throat, non-productive cough with rapid progression to LRTI as defined by new infiltrate on chest X-ray, signs on chest auscultation or hypoxia, especially in immunocompromised individuals, with increased risk of respiratory failure and potentially fatal outcome.[1] Allogeneic HSCT recipients are more likely to develop RSV LRTI if they have received a mismatched/unrelated transplant, a myeloablative conditioning regimen, or are elderly and lymphopenic at the time of the infection.[5]

Management of RSV infection is challenging with limited treatment options available. The most frequently used include ribavirin, intravenous immunoglobulin (IVIg) and palivizumab.[6] HSCT recipients with RSV infection have been treated with systemic or aerosolized ribavirin, alone or in combination with IVIg. The concomitant administration of IVIg and ribavirin is problematic in the UK, due to the restrictions imposed by the National Demand Management Programme for Immunoglobulin. The most recent update to the Clinical Guidelines for Immunoglobulin Use recognize the potential benefit of IVIg administration in solid organ transplant (heart and/or lung) recipients with viral pneumonitis including RSV, but do not include HSCT recipients in the same category.[4] Palivizumab is not licensed for use in adults and carries a high cost burden.

Ribavirin is a guanosine analogue currently used in the treatment of RSV. It is available in three different formulations: aerosolized, intravenous (IV), and oral; however, each preparation presents certain limitations.

Aerosolized ribavirin has a laborious and time-consuming administration which requires isolation measures and special attention due to teratogenicity.[7] Side-effects include claustrophobia, bronchospasm, and exacerbation of dyspnoea which requires caution in patients with asthma or chronic obstructive pulmonary disease. The IV formulation is very expensive and efficacy data are limited. Oral ribavirin is more cost-effective and easier to administer, does not require hospital admission, and has minimal side-effects. Recent UK guidelines have suggested oral ribavirin as an alternative to aerosolized ribavirin due to difficulties in accessing the aerosolized preparation.[7,8] The easy access to oral ribavirin and its suitability in the outpatient setting, correlated with the difficulties in obtaining the aerosolized formulation in the UK, make oral ribavirin the ideal choice.

A detailed literature review identified a limited number of publications on RSV infection and oral ribavirin treatment. Marcelin *et al.* analysed 15 allogeneic transplant patients treated using ribavirin dosed at 800 mg twice daily for patients >75 kg and 600 mg twice daily for adults <75 kg.[9] Casey *et al.* studied the outcome of 13 allogeneic HSCT recipients who had ribavirin administered at a daily dose of 10 mg/kg with the possibility to escalate up to 60 mg/kg depending on response and patient tolerance.[10] Khana *et al.* analysed 26 patients, a combination of allogeneic and autologous HSCT recipients, and used a different dosing regimen again: 10 mg/kg as a loading dose on day 1, followed by 400 mg three times daily on day 2, then continuation with 600 mg three times daily thereafter.[3] In this group, palivizumab was also administered to at least half the patients. The European Conference on Infection in Leukaemia (ECIL-4) guidelines published in 2013 suggest a ribavirin total daily dose of 10–30 mg/kg administered in three divided doses, with dose adjustments in renal impairment.[1]

In this study we report on the effective use of oral ribavirin in allogeneic HSCT recipients.

Methods

A retrospective analysis was conducted on 23 consecutive RSV patients treated with oral ribavirin between December 2010 and February 2015 in a single UK centre. Patients were identified from the virology department database and data were collected from the medical records, following approval from the hospital audit committee (audit number 6041).

Respiratory syncytial virus diagnosis was established by real-time polymerase chain reaction (PCR) assay, performed weekly on nose and throat swabs as active surveillance in inpatients, as a screening method in the pretransplant period and in outpatients with coryzal symptoms. PCR results were received within 24–48 h and treatment was initiated within 12–24 h of receipt of the result.

Oral ribavirin was initiated at a dose of 15 mg/kg divided into three daily doses for 10 days, with no subsequent dose escalation, as per centre policy. The 10-day course was extended in persistently symptomatic patients and treatment was escalated to aerosolized ribavirin in those who progressed to LRTI.

Results

Patient characteristics

This study analysed 23 HSCT recipients (male 12) with a median age of 52 years (range: 20–69 years); their HSCT characteristics are listed in Table I. There were 16 volunteer unrelated donors, six matched related donors, and one cord blood.

The prevalence of RSV infection at our institution was 16% (46 RSV infections in 280 autologous and allogeneic HSCT performed in the timeframe studied) which is comparable to the published literature.[6] All 23 patients in this study were diagnosed as outpatients and received oral ribavirin. Nevertheless, from the total of 46 RSV infections in both autologous and allogeneic HSCT recipients, treated with ribavirin in a different formulation than oral, i.e. aerosolized or IV and therefore not meeting the criteria for inclusion in the study, we identified that 28% (13/46) had contracted RSV infection in hospital.

All patients with a positive RSV PCR result received treatment promptly. At diagnosis, seven patients presented with LRTI, whereas 16 had an URTI. All patients received oral ribavirin at a dose of 15 mg/kg/day divided into three doses with no subsequent dose escalation performed, as per centre policy. The patients with LRTI were beyond the first month post-HSCT (range: 2–18 months), and were felt to be clinically stable, therefore oral treatment was deemed appropriate. Of note is that two out of seven in the LRTI subgroup continued on