Incidence and Outcomes of Respiratory Viral Infections in Pediatric Recipients of Allogeneic Hematopoietic Cell Transplant

Introduction

Background and Rationale:
Since its introduction in the 1960's as a potential treatment for various bone marrow failure syndromes and hematologic malignancies, allogeneic hematopoietic cell transplantation (Allo-HCT) has become a viable option for curative therapy of a wide array of diseases. Unfortunately, despite the substantial improvements in the clinical use of Allo-HCT, there remains a significant amount of morbidity and mortality associated with this treatment option. Of these potential complications, one which has become increasingly problematic is the role of common respiratory viral infections (RVI) in the first months to years after transplantation. While some of the viral infections discussed in this article would normally pose a minimal threat to the well-being of a healthy, immunocompetent host, those children who receive Allo-HCT are left severely immunocompromised for an extended period of time, often require immunosuppressants for an even longer duration of time, and often have underlying organ damage from their sometimes extensive chemotherapy or oncologic histories. This puts them at an extreme risk for severe complications from these seemingly benign viruses.

In a prospective multi-center study performed in 2001, Ljungman, et. al. demonstrated that RVIs are indeed a significant cause of morbidity and mortality. In his study, 1,973 recipients of stem cell transplants were analyzed for RVIs. Of those, 893 were Allo-HCT recipients and 3.5% of those patients were diagnosed with RVIs during the study period. The RVI-related mortality of the cohort was 1.1% - a significant portion of those diagnosed with RVIs. The most dangerous infections in this study were RSV (30.4% mortality) and Influenza (23% mortality). [1]

Multiple follow-up studies have been performed but two in particular focus on the questions we are planning to analyze with our study.

In a 14 year retrospective review of all Allo-HCT patients diagnosed with RSV from a single institution, Shah, et. al. demonstrated significant differences amongst three groups of patients classified based on an immunodeficiency scoring index. In this study, 237 Allo-HCT patients were diagnosed with RSV infection. They were split into groups based on a scoring index which factored neutropenia or lymphocytopenia, age, GVHD, steroid use, engraftment status, and type of conditioning regimen to determine risk for poor outcome. In this study, a statistically significant trend for increasing mortality and progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) was seen in the low risk group (0% and 7%, respectively), moderate risk group (3% and 15%, respectively), and high risk group (29% and 48%, respectively). [2]

In a 4 year retrospective review of Allo-HCT patients at a single institution, Wollfromm et. al. studied the incidence and outcomes of various RVIs. In this study, 131 of 378 (40%) recipients of Allo-HCT were diagnosed with RVIs for a total of 166 infections (including second infections in some patients). The likely reason for the significant difference in incidence between this and Ljungman's study described above lies in the use of PCR for detection of virus in symptomatic

patients as compared to the use of culture or DFA in the former study. Wollfromm separated his cohort by type of viral infection: disseminating infections (adenovirus), flulike infections (influenza, parainfluenza, respiratory syncytial virus, and metapneumovirus), and common cold infections (rhinovirus and coronavirus). In this study, there was a significantly higher incidence of common cold infections than flulike infections and a significantly higher incidence of these than adenovirus. In this study, 10% of RVI patients died and 5% had deaths attributed directly to their RVI. In this study, host immune status (similar to the measures described in Shah's study) were found to be significant risks for mortality, but no difference was identified by type of infection. That said, there was an insignificant trend towards increased incidence of hypoxemia in patients with adenovirus (25%) vs. flulike illnesses (12%) vs. common colds (6%).[3]

Aims

The primary aim of our study will be to analyze the risk factors - both factors relating to host immune function and factors relating to viral pathogenicity - for complications from viral infections in pediatric recipients of allogeneic hematopoietic cell transplantation.

The secondary aim of our study will be to analyze the incidence and outcomes of VRIs in pediatric recipients of allogeneic hematopoietic cell transplantation.

Hypothesis

We predict that patients who contract RVIs with poorer immune function will have worse outcomes than those with better immune function. We additionally predict that within these subgroups classified by immune status, those who contract adenovirus will have worse outcomes than the flulike RVIs (influenza, parainfluenza, human metapneumovirus or respiratory syncytial virus), which will have worse outcomes than those who contract the common cold RVIs (coronavirus, rhinovirus, or enterovirus).

Special Considerations: Of note, a potential confounding factor in our study will be the use of antivirals in our study. Whereas it is not standard of care to utilize aerosolized ribavirin for the treatment of respiratory syncytial virus or parainfluenza, it is utilized upon diagnosis of URTI or LRTI in all recipients of Allo-HCT at our institution. Additionally, as is the standard of care, all All-HCT patients diagnosed with influenza are treated with oseltamivir upon diagnosis of URTI or LRTI. These antiviral treatments may interfere with our data in that patients with these viral illnesses which we are considering high risk may actually have better outcomes than predicted.

Methods

Data to Be Collected:

- Patient name/MRN
- Type of RVI
- Method of diagnosis for RVI
- Age of patient at time of RVI diagnosis
- Days between transplant and RVI diagnosis
- Indication for transplant
- Conditioning regimen
- Stem cell source
- RVI diagnosis before or after engraftment
- Presence of acute graft-versus-host disease
    - Organ involvement, stage, and grade of acute GVHD
- Presence of chronic acute graft-versus-host disease
    - Organ involvement, stage, and grade of chronic GVHD
- Immunosuppressants at time of RVI diagnosis (if any)
- Absolute neutrophil count at time of RVI diagnosis
- Absolute lymphocyte count at time of RVI diagnosis
    - Most recent T cell panel may be more useful if available within 30 days prior to RVI diagnosis
- Intervention taken for treatment of RVI (antiviral therapy)
- Presence of URTI or LRTI at diagnosis of RVI
- Progression from URTI to LRTI
- Time until evidence of clearance of infection or resolution of symptoms
- Escalation of respiratory support (CPAP or BiPAP)
- Admission to ICU
- Need for Intubation
- Mortality
- Recurrence of RVI

Conceptual and Operational Definitions:

Upper Respiratory Tract Infection (URTI) will be defined as the onset of rhinorrhea, nasal or sinus congestion, otitis media, pharyngitis, cough with or without expectoration and with a positive viral culture, direct fluorescent antibody assay, or viral polymerase chain reaction obtained from nasal swab.

Lower Respiratory Tract Infection (LRTI) will be defined as clinical signs and symptoms of bronchiolitis or pneumonia (cough, hypoxia, respiratory distress, and/or fever, with new or changing infiltrates on chest radiography or computed tomography), along with positive viral culture, direct fluorescent antibody assay, or viral polymerase chain reaction obtained from a respiratory sample (nasal swab, throat swab, sputum, bronchoalveolar lavage fluid, endotracheal aspirate, biopsy specimen, or autopsy specimen).

Mortality will be assessed as death within 60 days of diagnosis. It will be attributed to the RVI if there is evidence of persistent or progressive viral infection with respiratory failure at the time of death or if death is deemed to be secondary to a complication of the RVI.

Statistical Analysis:
In order to obtain statistical significance for progression to LRTI, we assumed a prevalence of 25% in the adenovirus group, 10% in the flulike group, and 5% in the common cold group of RVIs, based on the results of the Wollfromm study. As such, to demonstrate statistical significance for worse outcomes in the adenovirus group versus the common cold group, we need 58 patients in each group (assuming equal prevalence), or 31 in the adenovirus group and 124 in the common cold group (assuming a prevalence of common cold infections four times that of the adenovirus group). To demonstrate statistical significance for worse outcomes in the adenovirus versus the flulike group, we would need 113 patients in each group (assuming equal prevalence) or 64 in the adenovirus group and 256 in the flulike group (assuming a prevalence of flulike infections four times that of the adenovirus group). To demonstrate statistical significance for worse outcomes in the flulike group versus the common cold group, we would need 474 patients in each group (assuming equal prevalence).

It is unlikely that we will be able to obtain such large numbers of patients for this retrospective study. We expect to study approximately 200-250 patients each from the flulike and common cold groups and roughly 50-70 patients from the adenovirus group.

Using our data, we will perform logistic regression analyses to determine the greatest risks for progression to LRTI, need for escalation of respiratory support to CPAP or BiPAP, need for intubation, and mortality. We will then perform Chi-squared analyses on the three subgroups of patients defined by the Immunodeficiency Scoring Index proposed by Shah, et. al.[2] to determine if viral pathogenicity has an impact on outcome in patients with similar immune function.

Subject Selection

Inclusion Criteria:
Our study will include patients aged 21 years or younger who received Allo-HCT who have been diagnosed with a respiratory viral infection via the methods identified above from the time period between January 1, 2001 and July 31, 2014. All data will be collected via retrospective chart review without need for direct patient interaction.

Miscellaneous

Confidentiality of Study Data:
The data will be collected and saved on a Microsoft Excel spreadsheet which will be password-protected and saved on an encrypted drive provided by the hospital's Information Technology department. Patients will not be contacted for any purpose relating to this study.

Investigators:

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References:

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3. Wollfromm A, Porcher R, Legoff J, et al. "Viral Respiratory Infections Diagnosed by Multiplex PCR after Allogeneic Hematopoietic Stem Cell Transplantation: Long-Term Incidence and Outcome." *Biol Blood Marrow Transplant* 2014; 1-4.