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Mini-review

Parainfluenza virus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: A systematic review

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ABSTRACT

Parainfluenza viral infections are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status and susceptibility to lower respiratory tract infections. Advances in diagnostic methods, including polymerase chain reaction, have led to increased identification and awareness of these infections. Lack of consensus on clinically significant endpoints and the small number of patients affected in each cancer institution every year make it difficult to assess the efficacy of new or available antiviral drugs. In this systematic review, we summarized data from all published studies on parainfluenza virus infections in HM patients and HCT recipients, focusing on incidence, risk factors, long-term outcomes, mortality, prevention, and management with available or new investigational agents. Vaccines against these viruses are lacking; thus, infection control measures remain the mainstay for preventing nosocomial spread. A multi-institutional collaborative effort is recommended to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

Introduction

Advances in diagnostic methods, including polymerase chain reaction (PCR), have led to increased identification and awareness of paramyxoviruses. Parainfluenza viruses (PIV) are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status. PIV is an enveloped, single-stranded RNA paramyxovirus; it is comprised of four antigens that share serotypes, but most clinical infections are caused by types 1, 2, and 3. A wide range of PIV incidence is reported in HM patients and HCT recipients. PIV type 3 is responsible for up to 90% of infections; it most commonly affects the upper respiratory tract after an incubation period of 1–4 days. Clinical manifestations include croup, otitis media, upper respiratory tract infection (URTI), bronchitis, pneumonitis, and less frequently, central nervous system infection. One of the most common complications of PIV URTI is progression to lower respiratory tract infection (LRTI), which occurs in 20%–39% of HCT recipients and has an associated mortality rate of up to 30% [1,2]. Whether treating these infections with available (ribavirin) or investigational (DAS 181) antiviral agents affects progression to pneumonitis or mortality remains unknown.

Many conflicting reports exist about the clinical disease spectrum, management, and overall outcomes of PIV infections in HM patients and HCT recipients. Hence, we conducted a systematic review of all published studies to determine the incidence, risk factors, management, long-term outcomes, and mortality rates associated with PIV infections in HM patients and HCT recipients. Advances in diagnostic methods, available or new investigational drugs, and vaccines are also discussed.

Materials and methods

Search strategy and selection criteria

We conducted an electronic literature search using Medline via the Ovid, Embase, Web of Science, and Cochrane library databases in September 2015. The following Medical Subject Heading terms were used: *human parainfluenza virus 1*, *human parainfluenza virus 2*, *human parainfluenza virus 3*, *human parainfluenza virus 4*, *hematopoietic stem cell transplantation*, *bone marrow transplantation*, *leukemia*, *lymphoma*, *multiple myeloma*, and *hematologic neoplasms*. The references in all of the selected studies were also reviewed to identify additional articles that did not appear in the initial search. The full texts of the selected articles were reviewed by all the authors. Inclusion and exclusion criteria were defined *a priori*.

Inclusion criteria selecting the articles were:

1 HM patients and HCT recipients of any age and had been infected with laboratory diagnosed PIV infection,
2 Retrospective or prospective observational studies and randomized controlled trials, if any, and
3 No time restriction for the study period.
4 Articles in English

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Exclusion criteria were:

1 Studies not focusing on PIV infections in HM patients or HCT recipients,
2 Review papers or meta-analyses,
3 Case reports of 10 patients or less
4 Meeting abstracts
5 Studies with duplicate data or incomplete information

We also searched the Clinical Trials registry (U.S. National Institutes of Health, www.clinicaltrials.gov) to identify any registered clinical trials for PIV infections.

Definitions

PIV infections and subsequent outcomes were ascertained by the authors of the original articles using various definitions; however, below are the summarized versions of these definitions used for the current review.

PIV case: Patients with a positive nasal wash, nasopharyngeal swab, or bronchoalveolar lavage for PIV by one of the viral diagnostic tests (viral culture, direct immunofluorescence testing, or PCR) were included in this review.

PIV-LRTI: Was defined as the onset of respiratory symptoms with new or changing pulmonary infiltrates, as seen on chest x-ray or CT scan of chest and/or virus isolated from lower respiratory samples (e.g., endotracheal tube aspirate, sputum, or bronchoalveolar lavage fluid).

PIV-mortality: Death was attributed to PIV if a persistent or progressive infection with respiratory failure was identified at the time of death.

Data abstraction

Two authors (D.P.S. and P.K.S.) independently screened the abstracts using predefined inclusion and exclusion criteria. Three authors (D.P.S., P.K.S. and J.M.A.) used standardized coding rules to abstract important variables from the final list of articles independently and discrepancies were resolved by discussion. Primary variables of interest for this study were incidence of PIV infection, progression of PIV-URTI to PIV-LRTI and PIV-associated mortality. Antiviral therapy included ribavirin (aerosolized, intravenous, or oral) alone or in combination with intravenous immunoglobulin (IVIG). Effect of antiviral therapy was measured by comparing incidence rates of these outcomes in treated and untreated patients. Outcome data from selected full-text articles were validated by R.F.C. For studies reporting outcomes in HM patients and HCT recipients, the data abstraction was split into two parts to capture the characteristics and outcomes of each group, respectively.

Statistical analysis

Agreement between the two independent authors in the first and second phase of the full-text selection process was checked by calculating Cohen's Kappa. Outcomes (i.e., LRTI progression and death) were descriptively summarized as percentages. We compared treated and untreated patient outcomes using Chi-squared or Fisher's exact tests, as appropriate. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). Forest plot was constructed to demonstrate the significant risk factors associated with acquiring PIV infection, PIV-LRTI and PIV-mortality using adjusted odds ratios from published studies. All statistical analyses were performed using STATA software version 13 (STATA Corp., College Station, TX, USA).

Results

We reviewed 441 abstracts on PIV infections in HM patients or HCT recipients. Of these, 274 were not specific to PIV infection or the pre-defined population or focus of the study. Of the remaining 167 abstracts, 101 were excluded from further review (49 were review studies on respiratory viruses, 12 were outbreak investigations, 24 were case reports with ≤10 patients, and 16 had overlapping data with an included study, had incomplete information, or were meeting abstracts); thus, we included 66 full-text articles. Twenty one studies measured the incidence of respiratory viruses in HM patients or HCT recipients and 11 studies provided primary data for LRTI risk factors and management and mortality, including antiviral therapy effects; thus, data were abstracted for PIV incidence, PIV-LRTI, and associated mortality. Furthermore, we reviewed studies that evaluated new diagnostic methods (9) and investigational new drugs (4); long-term outcomes such as airflow obstruction (6); prophylaxis (2); and pathophysiologic and immunogenetic factors (14). (A detailed flowchart of the abstract screening process is shown in Supplementary Fig. S1.) The agreement between the two authors during the selection of abstracts and the selection of full-texts, as measured by Cohen's Kappa, was 0.903 [95% CI: 0.862–0.945] and 0.926 [0.867–0.984], respectively, which is regarded as substantial to excellent.

Incidence of PIV infections

A total of 32 studies were reviewed, including 2 studies [1,3] that were divided into two parts to stratify information on HM patients and HCT recipients. Majority of the studies did not provide the breakdown for the type of HM for their study population; however, we observed that the most common HM for children was acute lymphoblastic leukemia (>60%). This information was not available for studies with adult patients. The incidence of PIV infections is displayed in Table 1. We identified 1196 PIV infections in 31,730 patients, giving an incidence of 4%, with a wide range of 0.2%–30%. The reported incidence of PIV infections in HCT recipients (4% [838 of 21,062]) was significantly higher than that in HM patients (2% [246 of 9,685]) (OR: 1.6; 95% CI: 1.4, 1.8; P value < 0.0001). Furthermore, a significantly higher PIV infection rate was reported in allogeneic HCT recipients (5% [482 of 10,147]) than in autologous HCT recipients (3% [206 of 7365]) (OR: 1.73; 95% CI: 1.46, 2.05; P value < 0.0001).

The significant risk factors for acquiring PIV infections in HCT recipients and HM patients are displayed in Fig. 1. Adults who underwent HCT from a matched unrelated donor or mismatched related donor had a significantly higher risk of PIV infection than did those who underwent matched related or autologous HCT [27,36]. Similarly, children who underwent allogeneic HCT or total body irradiation were more likely to acquire symptomatic infections, when adjusted for other variables [6]. In children with HM, age less than 2 years (OR: 2.69, 95% CI: 1.5–4.8) and having ALL rather than other malignancies (OR: 4.13, 95% CI: 2.37–7.21) were significant risk factors for PIV infections [30].

PIV-LRTI

The incidence of PIV-LRTI in HM patients and HCT recipients, as reported in 28 studies, is shown in Table 1. We identified 428 PIV-LRTI cases among 1163 PIV infections, giving an incidence of 37% for all studies combined (range, 0%–74%). Stratified by the underlying condition, PIV-LRTI was observed in 95 of 246 HM patients (39%) and 299 of 837 HCT recipients (36%) with PIV infections. PIV-LRTI incidence information was not available for different types of HCT.

The risk factors for PIV-LRTI are shown in Fig. 1. In brief, allo-HCT [10,27], especially infection within 100 days after HCT [6], lymphocytopenia [6,30], neutropenia at the onset of infection [1,6,30], use of corticosteroids during PIV-URTI [6,21], and respiratory co-infections [1,31] were significant predictors of LRTI progression.

PIV-associated mortality

Twenty six studies reported PIV-associated mortality in HM patients and HCT recipients (Table 1). This rate varied greatly, ranging from 0% to 31%, with a total of 117 PIV-deaths in 1138 PIV infected patients (10%). It was not significantly different in HCT recipients (12% [96 of 826]) than in HM patients (7% [16 of 230]); OR: 1.75; 95% CI: 1.0, 3.3; P value = 0.05). However, significantly higher mortality rate was observed in patients with PIV-LRTI (27% [117 of 428]; OR: 3.3, 95% CI: 2.4, 4.4, P value < 0.0001), irrespective of the underlying condition.

PIV-LRTI has been found to be a major risk factor for PIV-associated mortality in both HM patients and HCT recipients, irrespective of age [6,27,31]. Other risk factors are displayed in Fig. 1 and include lymphocytopenia [6,31], younger age [27], allo-HCT or mismatched related allo-HCT [10,27], refractory or relapsed underlying malignancy [1], APACHE II score >15 [1], respiratory