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Original article

Pneumococcal polysaccharide vaccination in allogeneic hematopoietic stem cell transplantation recipients: a prospective single-center study

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Abstract

Few studies have evaluated the response of allogeneic hematopoietic stem cell transplantation [allo-HSCT] recipients to pneumococcal polysaccharide vaccine-23 [PPSV23] in the modern transplant era when more elderly patients undergo allo-HSCT. We administered a single dose of PPSV23 to 30 allo-HSCT recipients and evaluated serotype-specific antibody responses using IgG measured by enzyme-linked immunosorbent assay and opsonophagocytic assay [OPA] titers in a multiplexed opsonophagocytic killing assay. The median patient age was 54 years [range, 23−68], and the interval from allo-HSCT to vaccination was 756 days [range, 389−1903]. No severe adverse effects were observed. The median positive response rates at 1 month and 1 year post-vaccination for the 7 serotypes measured by IgG were the same at 43% [range, 33−57], while those for 8 serotypes measured by OPA were 72% [range, 55−86] and 55% [range, 52−62], respectively. Peripheral blood stem cell transplantation improved vaccine response based on OPA titers at 1 month post-vaccination. During the median follow-up period of 1135 days post-vaccination, one patient developed pneumococcal bacteremia at 998 days. Our study suggests that PPSV23 vaccination in allo-HSCT recipients is safe and may result in a serological response.

Keywords: Hematopoietic stem cell transplantation; Pneumococcal vaccine; Vaccine potency

1. Introduction

Allogeneic hematopoietic stem cell transplantation [allo-HSCT] recipients are at high risk of invasive pneumococcal disease [IPD] owing to acquired deficiencies in humoral immunity [1]. In one prospective population-based study in Canada, the incidence density of IPD was 590 per 100,000 allo-HSCTs per year, compared with 11.5 per 100,000 persons per year in the general population [2]. Previous surveys have demonstrated the high fatality rate of IPD [13−20%] in allo-HSCT recipients [2−4].

Vaccination against pneumococcal disease is an important preventive strategy [1]. Currently, there are two types of pneumococcal vaccine available: a pneumococcal polysaccharide-based vaccine [PPSV] and a pneumococcal conjugate vaccine [PCV]. Compared to PPSV23 [covering 23 serotypes], PCV is highly immunogenic as a result of stimulating T cell−dependent antibody responses in the setting of incomplete immune reconstitution [5−7]. For this reason, PCV is recommended globally for allo-HSCT recipients [1,8].

In Japan, PCV7 [covering 7 serotypes] was introduced for children in October 2009, and PCV13 [covering 13 serotypes] was introduced in November 2013. A subsequent

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surveillance study performed from April 2013 through March 2015 demonstrated that the percentages of IPD caused by vaccine serotypes including PCV7 and PCV13 were 12% and 46%, respectively [9]. In contrast, PPSV23 still covers 66% of circulating serotypes in Japan [9]. Therefore, we hypothesized that PPSV23 might still play an important role in preventing IPD due to its broader serotype coverage. In addition, the development of allo-HSCT techniques such as reduced-intensity conditioning regimens has increased the possibility of performing allo-HSCT in elderly patients, whose immune responses to vaccines are generally markedly lower than in younger patients [10]. However, since the introduction of PCV in the 2000s there has been only one study of the efficacy of PPSV23 used alone in allo-HSCT recipients [5]. Therefore, we conducted this prospective study in order to evaluate the efficacy of a single dose of PPSV23 in allo-HSCT recipients in the modern era, when more elderly patients are undergoing HSCT and serotype replacement has become an issue.

2. Patients and methods

2.1. Study design

We conducted an open-label, single-arm study at the National Cancer Center Hospital from April 2012 through April 2013. The recipients who underwent allo-HSCT at our center were recruited and then administered a single dose of PPSV23. The study was conducted in compliance with the Declaration of Helsinki and was approved by the National Cancer Center Institutional Review Board. Informed consent was obtained from the recruited patients. The primary objective was to evaluate immune responses to PPSV23. The secondary endpoints included safety evaluation, factors affecting positive serotype-specific antibody response to PPSV23, and IPD cases during the follow-up period.

2.2. Eligibility

Patients aged 20–70 years with a hematological malignancy who underwent allo-HSCT at least one year earlier were enrolled in this prospective study. Exclusion criteria were platelet count $\leq$50,000 ml^{-1}; relapse of the underlying disease; active graft-versus-host disease [GVHD] requiring $\geq$0.3 mg kg^{-1} per day of systemic prednisolone; pneumococcal vaccination within the previous 5 years; known allergy to PPSV23; and immune globulin administration within the past 6 weeks.

2.3. Vaccine administration

We used commercially available PPSV23 [Pneumovax® NP, MSD, Tokyo, Japan] containing 25 μg each of 23 capsular polysaccharide types [1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F]. Each patient received a single vaccine dose [0.5 ml] subcutaneously in the upper arm.

2.4. Serum sample collection and antibody measurements

Serum samples were obtained before immunization and at 1, 6, and 12 months after vaccination. Collected samples were centrifuged at 1500 × *g* for 10 min and the serum samples were stored at −20 to −30 °C until analysis.

We measured concentrations of IgG against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F using an enzyme-linked immunosorbent assay [ELISA]. As a control, IgG against *Haemophilus influenzae* type b [Hib] was measured using ELISA. Antipneumococcal IgG antibodies were measured with a WHO-approved ELISA kit using a standard reference serum [89-SF] and C polysaccharide and 22F polysaccharide absorptions as previously described [11,12]. The levels of IgG specific to each serotype were determined according to the WHO protocol [a detailed protocol is available at www.vaccine.uab.edu/ELISAProtocol[007sp].pdf]. We also performed a multiplex-opsonophagocytic assay [MOPA], reported as the opsonophagocytic killing assay [OPA] titer for pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19A, 19F, and 23F. As controls, serotype 6C and Hib were measured using MOPA, which was performed using differentiated HL-60 cells and antibiotic-resistant target bacteria strains as previously described [13]. OPA titers were defined as the serum dilutions that led to 50% killing of target bacteria. Opsotitre 3 software [University of Alabama, Birmingham, Alabama, USA], an Excel-based data processing program, was used to convert colony counts to OPA titers, according to the WHO protocol available at www.vaccine.uab.edu/UAB-MOPA.pdf.

2.5. Safety assessments and definitions

Data on serious adverse events, deaths, and IPD after vaccination were collected from the day of PPSV23 administration through April 2015. Serious adverse events were identified according to clinical evaluations by treating physicians. Supportive care, including prophylactic antibiotic treatment, was given at the discretion of the primary doctors. IPD was defined as the isolation of *Streptococcus pneumoniae* from any normally sterile site (e.g., blood or cerebrospinal fluid). GVHD was defined according to standard criteria [14]. A positive serotype-specific antibody response was defined as a $\geq$2-fold increase in IgG concentrations or OPA titers, or an increase above 8 in the OPA titers. We employed these generally used thresholds because they are the best and most commonly used indicators at present, as previously reported [15,16].

2.6. Statistical analysis

Univariate analysis was performed using the Fisher's exact test to analyze the relationship of serotype-specific antibody response to factors that may influence it. All *P*-values were 2-sided and *P*-values of 0.05 or less were considered statistically significant. All statistical analyses were performed with EZR [Saitama Medical Center, Jichi Medical University, Saitama,

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