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Pertussis Immunity and Response to Tetanus-Reduced Diphtheria-Reduced Pertussis Vaccine (Tdap) after Autologous Peripheral Blood Stem Cell Transplantation

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Pertussis is a highly contagious respiratory infection characterized by prolonged cough and inspiratory whoop. Despite widespread vaccination of children aged < 7 years, its incidence is steadily increasing in adolescents and adults, because of the known decrease in immunity following childhood immunization. In an effort to reduce pertussis in adolescents and adults, 2 vaccines containing tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) (BOOSTRIX and Adacel) were licensed in 2005 for use in adolescents, 1 of which (Adacel) contains less pertussis toxoid (PT) for use in adults. This study assessed pertussis titers in 57 adult survivors of an autologous peripheral blood stem cell transplantation (PBSCT; median age, 37.5 years), 28 of whom were subsequently vaccinated with Tdap containing 2.5 μg of PT (Adacel). The median time to Tdap administration was 3 years posttransplantation. Before vaccination, 87% of the patients lacked pertussis immunity. Only 2 of the 28 patients developed a >2-fold response to PT following vaccination with Tdap. These data suggest that autologous transplantation recipients are highly susceptible to pertussis and that immunization with 2.5 μg of PT induces an inadequate response. Prospective trials evaluating BOOSTRIX, containing 8 μg/dose of PT (approved for adults in December 2008) are warranted in this vulnerable population undergoing transplantation.

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INTRODUCTION

Bordetella pertussis, a gram-negative coccobacillus, causes an acute respiratory illness that in its classic form is characterized by 1-2 weeks of rhinorrhea and intermittent cough, followed by 4-6 weeks of spasmodic cough, posttussive vomiting, and an inspiratory whoop [1]. The majority of adults with this disease have a paroxysmal cough lasting more than 3 weeks, with posttussive vomiting reported in 27%-61% [2-4]. Up to 12% of infected adults aged > 65 years require hospitalization [3,5]. Despite widespread and effective vaccination of children against pertussis since the 1940s, pertussis remains endemic in the United States [1-4].

Over the last decade, the incidence of pertussis has steadily increased in adolescents and adults to an estimated incidence of 800,000-3.3 million cases/year [1-4]. In 2005, in an effort to reduce pertussis in this population, 2 vaccines containing tetanus toxoid (TT), reduced diphtheria toxoid (DT), and acellular pertussis toxoid (PT), BOOSTRIX (GlaxoSmithKline Biologicals) and Adacel (sanofi Pasteur), were licensed for use in the United States [6,7]. BOOSTRIX was initially approved for use in individuals aged 10-18 years, and Adacel was approved for individuals aged 11-64 years. Although both vaccines contain similar amounts of TT and DT, they differ in terms of PT content and, up until recently, indicated age range [8]. In 2006, the Advisory Committee on Immunization Practices recommended that all adolescents and adults receive a single dose of Tdap to replace the scheduled Td booster [2,3].

There are limited data on pertussis immunity following hematopoietic cell transplantation (HCT) and on the immunogenicity of Tdap in this patient

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population [9]. In the present study, we assessed residual pertussis titers in 57 adult survivors of autologous peripheral blood stem cell transplantation (PBSCT), as well as the response of the first 28 patients vaccinated with Adacel. The effect of diagnosis, age at transplantation, time to vaccination, and receipt of the CD20 monoclonal antibody (mAb) rituximab on pertussis titers and vaccine response was assessed.

MATERIALS AND METHODS

Patients

A waiver of authorization to conduct this study was approved by Memorial Sloan-Kettering Cancer Center's Institutional Review Board. The medical records of adult patients who remained disease-free for 1 year after autologous PBSCT performed between January 1, 2000, and June 1, 2007, for the treatment of Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), or oligodendroglioma were reviewed for assessment of pertussis titers and immunization with Tdap. Dates of vaccination and prevaccine and postvaccine titers were obtained from a prospectively maintained database and confirmed by retrospective chart review. Titers against PT and filamentous hemagglutinin (FHA) were available in 57 patients, 28 of whom had been vaccinated with Tdap (Adacel). Patient and transplant demographics are shown in Table 1. The patients underwent transplantation for HL (n = 29), NHL (n = 25), or oligodendroglioma (n = 3). The median age at transplantation was 37.5 years (range, 17.8-71.9 years). Patients with NHL were significantly older than patients with HL (median age, 54 years vs 34 years; $P < .001$). The most commonly used transplantation conditioning regimens were carmustine, etoposide, cytarabine, and melphalan (BEAM; n = 21) and cyclophosphamide, carmustine, etoposide with (n = 8) or without (n = 7) involved field radiation therapy. Twenty-one of 25 patients who underwent transplantation for NHL received the CD20 mAb rituximab before transplantation (n = 4), after transplantation (n = 8), or both before and after transplantation (n = 9). All patients received autologous PBSC obtained after mobilization with ifosfamide, carboplatin, and etoposide. The median $CD34^+$ cell dose was 5.4×10^6/kg (range, 1.2-26.0×10^6/kg).

All patients received Adacel, approved for individuals aged 11-64 years, containing 2.5 μg of detoxified PT, 5 μg of FHA, 3 μg of pertactin, 5 μg of fimbriae types 2 and 3, 5 Lf (limit of flocculation unit) of TT, and 2 Lf of DT.

Antibody Titers

Antibodies against TT (anti-TT), DT (anti-DT), PT (anti-PT), and FHA were measured by enzyme-linked immunosorbent assay (ELISA). The lower limit of detection was for 0.1 IU/mL for TT, 0.01 IU/mL for DT, 1 IU/mL for PT, and 1 IU/mL for FHA. Anti-TT and anti-DT titers were considered positive if > 0.15 IU/mL and > 0.01 IU/mL, respectively. Although there is no known protective level of anti-PT immunity [1], in most studies, a value of 5-8 IU/mL is considered positive [10-12]. Thus, in this study, a positive vaue was defined as > 5 IU/mL. Response to TT and DT was defined as a 4-fold rise in titer or seroconversion; partial response was defined as a ≥ 2- and < 4-fold rise in titer. Response to PT was defined as ≥ 2-fold increase in anti-PT antibody level.

Table 1. Patient and Transplantation Characteristics

	Total (n = 57)	Tdap Recipients (n = 28)
Age at PBSCT, years, median (range)	37.5 (17.8-71.9)	42.6 (17.8-71.9)
Age at vaccination, years, median (range)		45.1 (20.2-73.2)
Diagnosis, n		
HL	29	12 (11 evaluable)
NHL	25	15 (14 evaluable)
Oligodendroglioma	3	1 (1 evaluable)
Cytoreduction, n		
BEAM	21	13
CBV	15 (8 with involved field radiation therapy)	8
TLI/Cy/VP	11	1
Busulfan/thiotepa	3	2
Total body irradiation–containing regimen	4	1
Other	4	3
$CD34^+$ cells/kg, median (range)	5.4 (1.2-26.0) × 10^6	4.65 (1.2-26) × 10^6

PBSCT indicates peripheral blood stem cell transplantation; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; BEAM, carmustine, etoposide, cytarabine, and melphalan; TLI, total lymphoid irradiation; CBV, cerebral blood volume; Cy, cyclophosphamide.

Statistical Analysis

The Fisher exact test for qualitative variables and the Wilcoxon rank-sum test for quantitative variables were used for comparisons between groups. Only P values < .05 were considered statistically significant.

RESULTS

PT and TT titers were assessed in 57 patients at a median of 38 months (range, 10-90.7 months) after transplantation. Only 13.5% of the patients had an anti-PT > 5 IU/mL (Figure 1); approximately 50% had an undetectable titer (< 1 IU/mL). The median anti-PT and anti-FHA titer was 1 IU/mL and 8 IU/mL, respectively. There were no significant differences in titers based on age at transplantation, years post-transplantation, or diagnosis of HL versus NHL. Nineteen of the patients (33%) lacked protective

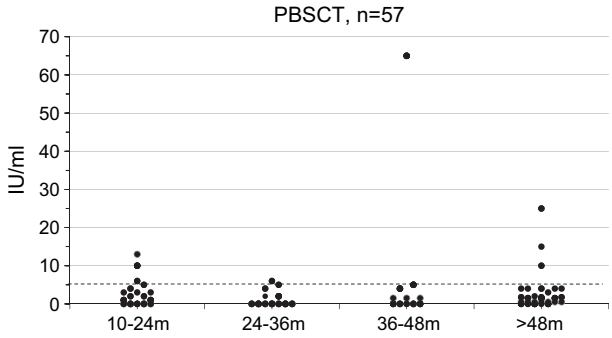

Figure 1. Pertussis titers after autologous PBSCT. The horizontal dashed line represents the lower limit of positive titers (> 5 IU/mL).

tetanus titers. Fourteen of the 40 patients (35%) tested for residual diphtheria immunity were seronegative.

Twenty-eight of the 57 patients (49%) were immunized with Adacel. In all 28 patients, both pretransplantation and postransplantation PT and TT titers were obtained. The median age at vaccination was 45.1 years (range, 20.2-73.2 years). The median time to vaccination was 36.0 months (range, 15.6-99.9 months) after transplantation. The median time to assess vaccine response was 87.5 days (range, 28-224 days) after Tdap administration. There was no significant difference in the time to vaccination in patients undergoing transplantation for HL or NHL (35 months vs 40 months). The median time between vaccination and the last dose of rituximab in the patients with NHL was 31.3 months. No patient reported a serious adverse reaction, including significant erythema, induration, or fever > 38.3°C. Before Tdap administration, 77% of the patients lacked immunity against pertussis, 24% lacked immunity against tetanus, and 28% lacked immunity against diphtheria.

Twenty-six of the 28 patients (93%) did not respond to PT. Two patients, 1 with an oligodendroglioma (aged 35 years) and 1 with NHL (aged 63 years), vaccinated 2.5 and 8.5 years posttransplantation, respectively, exhibited a > 2-fold response to PT. No patient with HL or any patient with NHL who received posttransplantation rituximab responded to PT or FHA. There was no difference in response rate when pertussis titers were assessed 1-3 months or 3-7 months after Tdap administration.

Despite the very poor response to PT and FHA, 6 of 12 patients with HL developed a partial (n = 1) or complete (n = 5) response (PR, CR) to TT, and 6 of 12 had a CR to DT. Response in patients with NHL, the majority of whom received pretransplantation and posttransplantation rituximab, was poor. Only 3 of 15 patients with NHL responded to TT (Figure 2). Of the 11 patients with NHL evaluated for response to DT, only 3 responded. There was a trend toward poorer TT response in patients undergoing transplantation for NHL compared with those doing so for HL ($P = .09$). The difference in DT response between these 2 groups was not significant ($P = .18$).

DISCUSSION

Disease-free survival (DFS) following autologous HCT for HL and NHL continues to improve, with increasing numbers of survivors reentering the workplace or school and caring for infants and young children [13-15]. Worldwide, more than 30,000 autologous HCTs are performed each year [16]. Without effective immunization practices, these patients are at risk for morbidity and mortality resulting from vaccine preventable disease and act as reservoirs to spread disease. In adults, particularly those over the age of 50 years, pertussis is associated with significant morbidity, including pneumonia and the need for hospitalization [3]. A study of 964 adults with pertussis, aged > 65 years found that 6% developed pneumonia and 12% required hospitalization [5]. Infected adults represent the major vector of pertussis for susceptible infants, the population with the highest morbidity associated with this disease [3]. Among 6114 children with

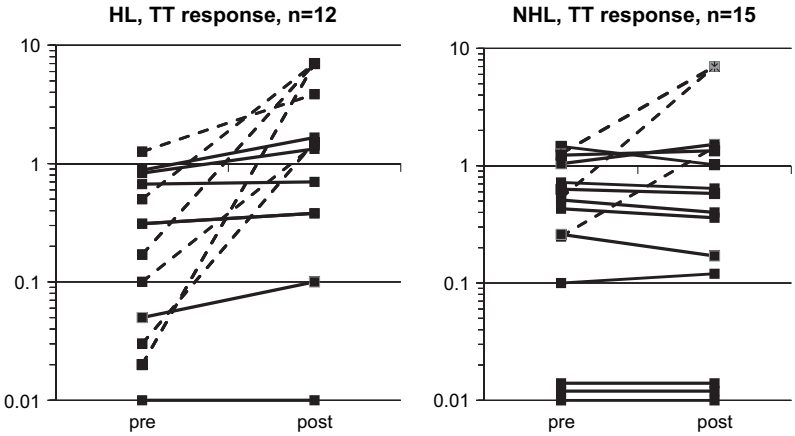

Figure 2. Tetanus titers before and after Tdap administration in patients after PBSCT for HL or NHL. The dashed lines represent patients who either seroconverted or developed a > 3-fold rise in tetanus antibody. Nonresponders are indicated by solid lines.

pertussis under age 12 months reported to the Centers for Disease Control and Prevention between 2000 and 2004, 62% required hospitalization and 13% developed pneumonia [3].

This study, the first to evaluate pertussis immunity following autologous HCT, demonstrates that long-term survivors of autologous PBSCT for lymphoma are highly susceptible to pertussis. In a study of healthy individuals aged 30-60 years, Launay et al. [11] reported that approximately 30% had anti-PT titers of 20-124 IU/mL, compared with < 2% in our study. This indicates either a lack of past infection in our patient population or, more likely, transplantation-related loss of pertussis immunity following childhood vaccination. More than 30% of our study population lacked detectable TT or DT titers posttransplantation. Studies of residual tetanus immunity after autologous HCT have shown variable results. Whereas Hammarstrom et al. [17] demonstrated that 71% (37/52) of autologous bone marrow (BM) recipients and 52% (20/38) of PBSC recipients were susceptible to tetanus by 1 year posttransplantation, none of the 35 adult recipients reported by Nordøy et al. [18] had become seronegative for tetanus when evaluated at 4-10 years posttransplantation, but only 36% of the 35 patients retained immunity against diphtheria. Clearly, differences in age at transplantation, underlying diagnosis, dose intensity, duration of treatment before transplantation, and the transplantation conditioning regimen influence the duration of residual titers as well as response to vaccination. Nevertheless, our study, as well as those of others [19], demonstrate poor response to a single Td or TT vaccine after autologous HCT. Gandhi et al. [19] reported that only 8 of 24 autologous PBSCT and 1 of 9 autologous BM transplantation recipients responded to a single tetanus immunization. These findings emphasize the need to give more than one tetanus- and diphtheria-containing vaccine to all recipients of autologous HCT recipients, as recommended in current posttransplantation vaccine guidelines [20,21].

The pertussis response in our study was poor regardless of age, diagnosis, or time posttransplantation. The lack of response to Tdap containing 2.5 ug of PT is likely due to insufficient numbers and/or function of antigen-specific memory T and/or B cells. In December 2008, the Tdap vaccine BOOSTRIX, containing 8 ug of PT, was approved for adults, extending its original indication beyond adolescence [8]. Our data suggest that this vaccine should be tested in autologous HCT recipients because of its higher PT content. Posttransplantation, even higher doses of PT and/or several immunizations may be needed to induce immunity. Although more than one vaccination with Tdap is not currently recommended for healthy individuals, vaccines containing > 8 ug of PT have been used safely in adults. In a study of 261 pediatric health and child care workers immunized with a single monovalent pertussis vaccine containing 25 μg of PT, long-lasting immunity was achieved in the absence of serious adverse events [10]. Median IgG anti-PT levels of 76, 71, 71, and 63 EU/mL were observed at 1, 2, 3, and 4 years, respectively, following a single dose. Prospective trials testing strategies to effectively immunize the growing numbers of autologous HCT survivors against pertussis are needed.

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