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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