

ORIGINAL ARTICLE

Inhaled corticosteroids stabilize constrictive bronchiolitis after hematopoietic stem cell transplantation

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Post transplantation constrictive bronchiolitis (PTCB) is the most common pulmonary complication among long-term survivors of allogeneic hematopoietic stem cell transplantation (HSCT). It is a late manifestation of GVHD. Its treatment with high-dose systemic corticosteroids and other immunosuppressive regimens is associated with multiple side effects. Topical corticosteroids are used for the treatment of other manifestations of GVHD to minimize these side effects. We conducted a retrospective analysis of a series of adult patients to evaluate the efficacy of high-dose inhaled corticosteroids in the treatment of PTCB. Seventeen patients with new-onset airflow obstruction were diagnosed with PTCB. Their forced expiratory volume in 1 s (FEV1) declined from a median of 84% (range, 56–119) before HSCT to 53% (26–82) after HSCT. All patients received inhaled fluticasone propionate 500–940 µg two times daily. Symptoms of airway obstruction improved and FEV1 stabilized 3–6 months after treatment. We conclude that high-dose inhaled corticosteroids may be effective in the treatment of PTCB and propose a plausible mechanism of its action. A prospective evaluation of its efficacy is warranted.

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Introduction

Hematopoietic stem cell transplantation (HSCT) is the only curative option for many patients with relapsed and

high-risk hematologic malignancies.¹ Long-term morbidities associated with HSCT, including chronic GVHD, are frequently seen.^{2,3} Post transplantation constrictive bronchiolitis (PTCB) is the most common pulmonary complication among long-term survivors that may lead to progressive respiratory insufficiency and even death.^{2–6} Due to the lack of uniform diagnostic criteria, the reported incidence of PTCB varies from 10 to 26%.⁴ The most commonly identified risk factors are chronic GVHD, older age, viral respiratory infections during the first 100 days after transplantation, airflow limitation before transplantation and low level of serum IgG.^{4,7} The pathophysiology of PTCB is not well understood, however, it is generally accepted that PTCB is a pulmonary manifestation of chronic GVHD.

There have been no prospective studies to evaluate different treatment options for PTCB. Treatment is usually reserved for chronic GVHD, and typically consists of augmenting systemic immunosuppression including corticosteroids.⁸ Prolonged use of systemic corticosteroids is associated with an increased risk of infection and other toxicities that may compromise quality of life and threaten survival. Topical corticosteroids are used in the treatment of other manifestations of GVHD to reduce the need for and the side effects associated with systemic treatment.^{9,10} Therefore, we hypothesized that high-dose inhaled corticosteroids would be efficacious in halting and possibly reversing airway obstruction in patients with PTCB. We report here the results of a retrospective study wherein we analyzed clinical factors associated with PTCB, and the beneficial effects of high-dose inhaled corticosteroids.

Methods

Patient selection and clinical data

We reviewed the medical records of adult patients who underwent allogeneic HSCT and were referred between January 2002 and July 2005 to the Department of Pulmonary Medicine at The University of Texas MD Anderson Cancer Center for treatment of airflow

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obstruction. PTCB was diagnosed if the following criteria were met: (1) new-onset airflow obstruction, (2) absence of infiltrates on chest radiological studies and (3) no evidence of new restrictive disease. The study was approved by the institutional review board with the waiver of informed consent. Medical records included electronic clinical notes; microbiologic reports; laboratory data and pulmonary function tests. Records were reviewed for possible risk factors such as age, underlying disease, and conditioning regimen and previous history of viral infections. Data about donors and histocompatibility matching status were collected. Laboratory data, including serum immunoglobulin (IgA, IgG, IgM) levels and eosinophil counts, were recorded. CMV reactivation, assessed by measuring pp65 antigen detection in peripheral blood neutrophils, was determined before HSCT and at regular intervals thereafter.

Corticosteroid therapy

All patients received high-dose fluticasone propionate 500–940 µg two times daily by oral inhalation. Doses were picked by the treating pulmonary physician. Other systemic immunosuppressive therapies were administered by the primary stem cell transplant physician as deemed necessary for the treatment of PTCB or other manifestations of GVHD. Pulmonary function tests were performed according to the American Thoracic Society guidelines.¹¹ Follow-up pulmonary function tests were performed 3–6 months after treatment with high-dose inhaled corticosteroids. Symptoms including shortness of breath, cough and wheezing were followed and documented by the treating physician.

Statistical analyses

PFT parameters were described by their median and range and were visually represented with line plots and box plots. The changes in PFT parameters from pretransplantation to post transplantation were assessed with a Wilcoxon signed rank test. Two-sided *P*-values of less than 0.05 were considered statistically significant. Analyses were carried out with SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

We analyzed data collected from the records of 17 patients who were referred to our department. Patient demographics and baseline characteristics are provided in Table 1. The median interval from HSCT to PTCB diagnosis was 10.5 months (range, 3–33), and the median follow-up period from HSCT was 32 months. All patients were allogeneic HSCT recipients, with four patients (24%) receiving prior autologous transplants, and two patients (12%) receiving more than one allogeneic stem cell transplant. As of 31 July 2005, all patients were alive except one who died of progressive respiratory insufficiency due to fungal pneumonia.

PTCB diagnosis and treatment

All our patients had a marked decrease in their FEV₁ at the time of pulmonary referral (median 84% (range, 56–119%)

Table 1 Characteristics of patients with PTCB

Mean age, years (range)	46 (26–63)
Males	11 (65)
Smoking history	8 (47)
History mantle radiation	2 (12)
<i>Underlying disease</i>	
Acute myelogenous leukemia	5 (29)
Chronic myelogenous leukemia	1 (6)
Chronic lymphocytic leukemia	1 (6)
Non-Hodgkin's lymphoma	5 (29)
Hodgkin's lymphoma	1 (6)
Multiple myeloma	1 (6)
Myelodysplastic syndrome	1 (6)
Aplastic anemia	1 (6)
Renal cell carcinoma	1 (6)
<i>Source of stem cells</i>	
Peripheral blood	12 (71)
Bone marrow	5 (29)
<i>Type of transplant</i>	
Matched related	8 (47)
Matched unrelated	5 (29)
Unmatched related	3 (18)
Unmatched unrelated	1 (6)
<i>Donor–recipient mismatch</i>	
One HLA antigen	4 (24)
ABO/Rh	10 (59)
Sex	6 (35)
<i>GVHD</i>	
Acute	8 (47)
Chronic	16 (94)
De novo	7 (41)
Limited	1 (6)
Extensive	16 (94)
Progressive	1 (6)
Relapsing	9 (53)
<i>Chronic GVHD organ involvement</i>	
Skin	13 (76)
Eyes	11 (65)
Gastrointestinal tract	7 (41)
Oral mucosa	7 (41)
History of respiratory viral infections ^a	9 (53)
<i>Patients with hypoglobulinemia</i>	
IgG < 624 mg/dl (measured in 15)	12 (80)
IgA < 74 mg/dl (measured in 13)	9 (69)
IgM < 29 mg/dl (measured in 14)	2 (14)

Abbreviation: PTCB = post transplantation constrictive bronchiolitis.

All values represent *n* (%) unless otherwise stated.

^aInclude respiratory syncytial virus, parainfluenza virus, influenza A virus, adenovirus, and herpes simplex virus.

at baseline to 53% (26–82) at diagnosis *P* < 0.001) (Figures 1a and b). Total lung capacity did not significantly change (97% (82–120) to 90% (70–143)), and the diffusing capacity for carbon monoxide mildly decreased (70% (56–113) to 61% (23–76)) (Figure 1c). After the start of high-dose corticosteroids, FEV₁ stabilized with tendency for improvement (61% (25–82) *P* = 0.057) (Figures 1a and b), median time for the follow-up PFT was 5 months (range, 3–7). The corticosteroids were well tolerated and improved the symptoms of airway obstruction including shortness of breath, cough and wheezing.

Risk factors

Common clinical factors in PTCB patients included chronic GVHD (94% of PTCB patients), low levels of serum IgG (80%), and viral respiratory infections (53%) Table 1. Most of our patients received peripheral blood stem cell transplants; with a minority receiving a mismatched-related

HSCT (4 (24%)). Fludarabine was the most frequently used drug for conditioning followed by cyclophosphamide Table 2. Eight patients (47%) developed acute GVHD, and nearly all of the patients (16 (94%)) developed chronic GVHD. The most frequently involved organs in patients with GVHD were the skin and eyes. Elevated absolute eosinophil counts at the onset of symptoms were seen in 14 patients (82%), with a mean value of 1176 cells/ μ l (reference range, 40–400 cells/ μ l). Only 2(12%) of our patients received immunoglobulin replacement therapy on a chronic basis. As for CMV reactivation, seven patients (41%) experienced CMV reactivation after undergoing HSCT, four (57%) of whom developed early reactivation within the first 100 days after transplantation and three (45%) developed late reactivation after 100 days. It is notable that the frequencies of individuals developing early and late CMV antigenemia were both lower than that typical of other allogeneic HSCT recipients at our center. We observed no clear temporal correlation between CMV reactivation and PTCB diagnosis. Nine patients (53%) had history of respiratory viral infections prior to the diagnosis of PTCB. These infections were caused by respiratory

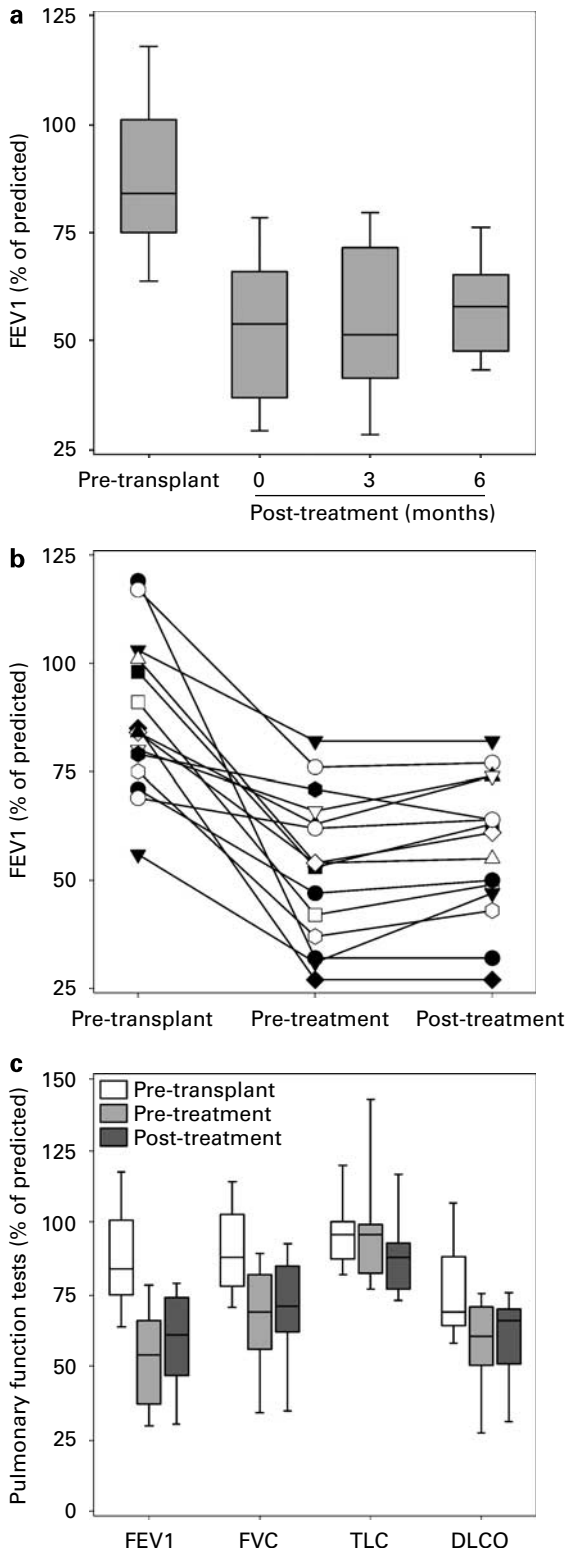


Table 2 Conditioning regimens and immunosuppressive treatment

Patients	Conditioning regimen	Immunosuppressive treatment
1	Cy/TBI	Tacrolimus/CS/photopheresis
2	Flu/Bu/ATG	Tacrolimus/CS/mycophenolate/photopheresis
3	CP/Flu/Ara-C	Tacrolimus/CS
4	Cy/Flu/ Rituximab	Tacrolimus/CS
5	Cy/Bu	Tacrolimus/CS
6	Flu/Mel/Gem	Tacrolimus/CS
7	Flu/Ara-C/Gem	Tacrolimus/photopheresis
8	Flu/Mel/ATG	Tacrolimus/CS
9	Cy/Flu/ Rituximab	Tacrolimus
10	Bu/Cy	Tacrolimus/CS
11	Flu/Mel	None
12	Flu/Cy/Campath/ Rituximab	None
13	Flu/Bu	Tacrolimus/CS
14	Flu/Bu/ATG	Tacrolimus/CS/mycophenolate
15	Flu/Cy/Campath/ Rituximab	CS
16	Flu/Mel/Campath	Tacrolimus/CS
17	Flu/Mel	CS

Abbreviations: ATG = antithymocyte globulin; CP = cisplatin; CS = corticosteroids; Flu = fludarabine; Gem = gemtuzumab ozogamicin; Mel = melphalan.

Figure 1 Serial pulmonary function test values. (a) Box plot shows FEV₁ values for patients before HSCT (pretransplant), at diagnosis of PTCB (pretreatment), and 3–6 months after treatment with high-dose inhaled corticosteroids (post treatment). (b) FEV₁ values for individual patients before HSCT (pretransplant), at diagnosis of PTCB (pretreatment), and 3–6 months after treatment with high-dose inhaled corticosteroids (post treatment). (c) Box plot shows FEV₁, FVC, total lung capacity, and diffusing capacity for carbon monoxide values for patients before HSCT (pretransplant), at diagnosis of PTCB (pretreatment), and 3–6 months after treatment with high-dose inhaled corticosteroids (post treatment). Each box plot shows the median (the horizontal line within the box), the interquartile range (horizontal line at either end of the box), and the 10th and 90th percentile (I bar).

syncytial virus (three patients), influenza A (three patients), parainfluenza (two patients), and herpes simplex virus (one patient). All these infections were diagnosed more than 100 days after HSCT, diagnosis was obtained either with nasal washes (six patients) or bronchoalveolar lavage (three patients). Other immunosuppressive therapy used for the treatment of PTCB or other manifestation of chronic GVHD included prednisone, Tacrolimus, and mycophenolate mofetil Table 2. Only three patients (18%) received photopheresis during that time, all of them had stabilization in their lung function.

Discussion

The clinical course of PTCB varies, but most patients eventually develop progressive disease that leads to irreversible airflow obstruction because of a lack of an effective standard treatment regimen. Systemic immunosuppressive therapy and cytotoxic medications have been tried, but improvement in lung function is limited. Furthermore, these treatments are based on anecdotal reports and on the opinion of experts but not on randomized controlled clinical trials that evaluated their potential benefits. Prolonged systemic immunosuppression is associated with significant morbidity and decreased quality of life. At 3–6 months after treatment with high-dose inhaled corticosteroids, the FEV₁ stabilized in nearly all of our patients (Figures 1a and b). The corticosteroids were well tolerated and relieved the symptoms of airway obstruction. In a retrospective review by Sanchez *et al.*¹² systemic immunosuppressive therapy resulted in 60% clinical benefit rate with only 30% showing complete response. Our results showed a clinical benefit in 94% of our patients. Despite the small sample size in both studies the difference in clinical benefit could be due to the addition of inhaled corticosteroids in our patients. Furthermore, a recent study by Bergeron *et al.*¹³ evaluated the effect of inhaled corticosteroids in combination with long-acting bronchodilators in patients with PTCB and showed significant improvement in their symptoms and their lung functions. All this suggests that inhaled corticosteroids could have a potential role in the treatment of this disease.

In agreement with other previously published studies,^{2,4,6,14,15} we found that nearly all patients who developed new-onset airflow obstruction after HSCT had chronic GVHD, suggesting that PTCB is a pulmonary manifestation of GVHD. Low levels of serum IgG and history of viral infections were also associated with this disease. Other risk factors found in previous studies such as older age, donor–recipient mismatch, and CMV positivity, were not highly prevalent in our series of PTCB patients.

Our results have several limitations. We were unable to evaluate the efficacy of inhaled corticosteroids as a steroid-sparing agent due to the limitations of a retrospective analysis, the small sample size, and the short follow-up period. Additionally, we did not use a formal assessment tool of respiratory symptoms, and we were unable to standardize a treatment regimen.

Understanding the pathophysiology of PTCB is crucial to assessing new therapeutic and prophylactic interven-

tions. To explain our results, we propose here a plausible etiology for PTCB and the mechanism of action of inhaled corticosteroids. Although the pathogenesis of GVHD is not clearly understood, it is believed that donor T lymphocytes play an important role in its acute and chronic phases with the predominance of T_H2 cytokines such as IL-4, IL-5, and IL-13 in the chronic phase.¹⁶ Various studies have shown a strong association between fibrogenesis, a hallmark of PTCB, and the development of a T_H2 CD4 inflammatory response that involves IL-4 and IL-13.^{17–20} Given the fact that PTCB is a form of chronic GVHD of the lung it is plausible that it is a T_H2-mediated disease, which may explain the clinical response we observed to inhaled corticosteroids. Furthermore, airway fibrosis can explain the limited improvement in FEV₁.²¹

Chronic GVHD continues to be a major contributor to mortality and morbidity in long-term survivors of HSCT. PTCB is an important contributor to this process. Chien *et al.*¹⁴ showed that new-onset airflow obstruction after HSCT is an important predictor of mortality. Our results suggest that treatment with high-dose inhaled corticosteroids may be highly efficacious in this population, while inducing fewer side effects. Furthermore, the finding that most of our patients had moderate to severe airflow obstruction at the time of presentation suggests that by the time symptoms develop, the disease is already advanced due to airway fibrosis resulting in irreversible obstruction. Therefore, prevention and early detection of PTCB are crucial to improve survival in this population. Prospective evaluation of the role of inhaled corticosteroids in prevention and treatment of this disease is warranted. Studies are urgently needed in this patient population to understand the pathogenesis of this disease, to identify various risk factors in preclinical models, and to initiate a targeted treatment to halt its progression.

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