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# Screening with Spirometry Is a Useful Predictor of Later Development of Noninfectious Pulmonary Syndromes in Patients Undergoing Allogeneic Stem Cell Transplantation

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Noninfectious pulmonary syndromes (NIPS) frequently complicate allogeneic stem cell transplantation (allo-SCT). The most common and serious is the bronchiolitis obliterans syndrome, characterized by irreversible fixed airflow obstruction, impaired quality of life, and a high mortality. Treatment for established symptomatic disease is relatively ineffective. We therefore sought to identify potential predictive factors for development of NIPS, which may identify patients at risk in whom earlier intervention may be of benefit. Spirometry and diffusing capacity for carbon monoxide were performed before allo-SCT, day 100, and 1 year after allo-SCT. We retrospectively analyzed spirometry in consecutive patients having allo-SCT from 2004 to 2010, along with computed tomography and bronchoalveolar lavage results to identify cases of NIPS. Cases of bronchiolitis obliterans syndrome were defined as per current National Institutes of Health consensus guidelines. Spirometry results and baseline variables were compared between patients with and without NIPS to identify early predictors and risk factors for NIPS. Of 235 assessable patients, 23 (9.8%) developed NIPS. Median time of onset was day 367 (interquartile range [IQR], 144 to 544 days). Changes in forced expiratory volume in 1 second (ΔFEV1.0) was the best predictor of later NIPS development. Median ΔFEV1.0 from pretransplant to day 100 in patients later developing NIPS was −12% (IQR, −25% to −1%) versus −1% (IQR, −7% to +6%) in unaffected patients, $P = .002$. From pretransplant to 1 year, ΔFEV1.0 was −19% (IQR, −37% to −6%) versus −3% (IQR, −10% to +4%) in patients later developing NIPS and unaffected patients, respectively, $P < .001$. Busulfan-based, but not total body irradiation–based, conditioning increased the risk of NIPS (hazard ratio, 9.4 [3.4 to 23.9], $P < .001$). No cases of NIPS were seen in the 53 patients who received in vivo T cell depletion with antithymocyte globulin (ATG, Genzyme Transplant, Cambridge, MA) ($P < .0001$). NIPS were associated with high transplant-related mortality relative to unaffected patients (hazard ratio, 6.6 [2.5 to 16.4], $P < .001$). Spirometry is a potentially useful screening test for identification of presymptomatic NIPS. We recommend 3-monthly spirometry surveillance for up to 2 years post-transplant. Our findings require prospective validation to identify patients in whom earlier intervention may potentially modify the natural history of this disease.



## INTRODUCTION

Pulmonary complications occur in 25% to 50% of allogeneic stem cell transplantation (allo-SCT) recipients, with 50% of these being noninfectious in etiology [1]. Of noninfectious pulmonary complications, both acute and subacute chronic disorders are recognized. The idiopathic pneumonia syndrome, which presents within the first 120 days postallograft, is associated with a fulminant course, poor response to therapy, and a high mortality of 60% to 80%. Although the precise etiology is unknown, idiopathic pneumonia syndrome is associated with grades III to IV acute graft-versus-host disease (aGVHD) [2].

Subacute and chronic noninfectious pulmonary syndromes (NIPS) may be divided into 2 distinct syndromes: bronchiolitis obliterans syndrome (BOS) and cryptogenic organizing pneumonia (COP) (formerly termed bronchiolitis obliterans organizing pneumonia or BOOP). BOS is an obstructive process that targets terminal bronchioles [3] characterized by an insidious clinical onset [4], fixed airflow obstruction on spirometry, and characteristic features on high-resolution computed tomography. Surgical lung biopsy is the gold standard but is not often performed because of a high complication rate [5]. BOS has a dismal prognosis, with a 5-year survival of approximately 13%, which has not improved significantly over the past 2 decades [4,6,7]. Only some symptomatic patients diagnosed with BOS have been shown to respond to therapy [7], although prospective clinical trials, including studies in which early intervention before development of symptomatic disease, have yet to be systematically undertaken. Using the 2005 National Institutes of Health

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consensus criteria [8], an analysis showed a 1.6-fold increase in mortality after diagnosis of BOS [9].

The precise etiology of BOS is unknown. BOS may represent a form of chronic GVHD (cGVHD), although biopsy specimens from patients with BOS do not show the characteristic epithelial cell apoptosis characteristically associated with GVHD in other organs [2]. The strong and consistent association between cGVHD and BOS in many observational studies, however, suggests a common immune etiology [6,9-14]. Additional evidence for an alloimmune basis for this disease includes the similarity between BOS and the clinicopathological syndrome that frequently develops after pulmonary allograft [15,16]. This latter syndrome has been shown to be initiated by alloimmunization [17-20]. In addition, the incidence of BOS in recipients of autologous SCT when conditioned with similar preparative regimens is rare [7].

Previously identified risk factors for BOS other than cGVHD include poor pretransplant lung function and older age [21], aGVHD [21], mobilized peripheral blood progenitor cells rather than a marrow stem cell source [22], pulmonary complications post-allograft [23] or idiopathic pneumonia syndrome [22], conditioning intensity [24], total body irradiation (TBI)-based conditioning, methotrexate for GVHD prophylaxis, busulfan treatment [22], female donor to male recipient [22], hypogammaglobulinemia [10], and viral infections in the first 100 days after allo-SCT [21]. Several studies have shown T cell depletion to be protective against cGVHD in general, as well as specifically reducing NIPS [23,25] or chronic lung dysfunction [26].

COP represents a distinct form of NIPS characterized by cough, fever, and dyspnea that is associated with peribronchovascular and subpleural alveolar infiltrates on computed tomography with plugs of granulation tissue in respiratory bronchioles and alveoli and chronic interstitial inflammation [14]. In the allograft setting, COP has superior outcomes compared with BOS and idiopathic pneumonia syndrome [14]. A strong correlation between both aGVHD and cGVHD and the development of COP has also been shown, although the precise etiology of COP, as with BOS, remains unknown.

Given the high morbidity and mortality rate of BOS, use of a predictive screening test to identify presymptomatic patients and institute early immunomodulatory therapy, which may prevent irreversible structural damage, is an attractive strategy. A paucity of published data surround the utility of screening with spirometry for predicting development of NIPS. It has been suggested that early declines in pulmonary function using the forced expiratory volume in 1 second (FEV1.0) measurement on spirometry are associated with increased risk of airflow obstruction at 1 year [27,28], cGVHD, and a poorer overall survival after allo-SCT [29], but these studies have not specifically addressed long-term adverse respiratory outcomes.

## METHODS

We sought to establish clinical predictive factors for the development of NIPS (defined as BOS or COP). At our institution, routine pulmonary function screening with spirometry was instituted in 2004, with patients investigated with pretransplant spirometry including measurement of diffusing capacity for carbon monoxide, followed by repeat measurements at day 100 (D100), 1 year, and 2 years. Because our primary focus was identifying whether spirometry pretransplant at D100 and 1 year is a useful predictor of the development of pulmonary complications, cases of idiopathic pneumonia syndrome were not considered in our analysis.

All patients had standard clinical and laboratory data prospectively collected in a central database, which was analyzed to determine whether early declines in lung function were predictive of later development of pulmonary dysfunction. Secondary objectives were the identification of risk factors for the development of BOS within our patient cohort.

### *Conditioning Regimens*

Patients included in this analysis received either myeloablative or reduced-intensity conditioning regimens. Myeloablative conditioning contained either TBI $\geq$ 12 Gy or busulfan $\geq$ 16 mg/kg orally or 12.8 mg/kg by i.v. infusion combined with cyclophosphamide 120 mg/kg. Most patients with acute lymphoblastic leukemia were conditioned with fractionated TBI 13.2 Gy and etoposide 60 mg/kg, with palifermin for mucositis prophylaxis.

Reduced-intensity conditioning regimens included fludarabine 125 mg/m$^2$ and melphalan 140 mg/m$^2$ or fludarabine 90 mg/m$^2$ and cyclophosphamide 2250 mg/m$^2$. Patients who received umbilical cord unit transplants were conditioned with either a myeloablative regimen of fludarabine 75 mg/m$^2$, cyclophosphamide 120 mg/kg, and 12 Gy fractionated TBI from day $-3$ to day $-1$ or a nonmyeloablative regimen of fludarabine 200 mg/m$^2$, cyclophosphamide 50 mg/kg, and 2 Gy TBI.

### *GVHD Prophylaxis*

GVHD prophylaxis at our institution was provided with cyclosporine and methotrexate. In cord transplants, mycophenolate mofetil 1 g twice daily was used in lieu of methotrexate. Before 2007, all patients also received prednisolone .5 mg/kg until day +35, followed by .25 mg/kg until day +49. In vivo T cell depletion was performed in selective cases with antithymocyte globulin; antithymocyte globulin (Fresenius, Fresenius Biotech GmbH, Munich, Germany) was used for patients with a serological mismatch at 1 of the major loci or selected higher risk patients with a molecular mismatch, at a total dose of 60 mg/kg. Since April 2007, T cell depletion has been performed for all matched unrelated donors (MUDs) or mismatched related donors using rabbit anti-human antithymocyte globulin (ATG) at a total dose of 4.5 mg/kg. After 2007, corticosteroid prophylaxis was used for sibling transplants only, with patients receiving MUD transplants instead receiving in vivo T cell depletion with Thymoglobulin, as outlined above, in addition to standard cyclosporine A and methotrexate.

### *Data Capture and Analysis*

Patients transplanted between 2004 and 2010 were deemed eligible for this study, with 257 patients identified and for whom clinicopathological data and respiratory function tests were examined. Patients with abnormal spirometry (FEV1.0 $<$ 75% predicted) developing post-transplant were identified; 23 patients were identified with BOS by National Institutes of Health criteria [8] or COP. All 23 patients had undergone bronchoscopy with bronchoalveolar lavage to exclude an infectious etiology. No patient had a surgical lung biopsy. GVHD was assessed according to established guidelines [30,31].

Descriptive statistics were used to identify differences in baseline characteristics between the group of patients who later developed NIPS and those who did not. Chi-square tests were used for categorical variables, whereas *t*-test or Mann-Whitney tests were used to test for differences for continuous variables that were normally distributed (age) and not normally distributed (total number of CD34$^+$ progenitors infused), respectively. Multivariate analysis was conducted using logistic regression including variables identified from the univariate as having a $P < .2$. Changes in FEV1.0 ($\Delta$FEV1.0) from baseline to D100, baseline to 1 year, and D100 to 1 year were calculated. Comparisons were made between the group who later developed GVHD of the lung and those who did not, using the log rank (Mann-Whitney) test, and receiver operator characteristic (ROC) curves were generated to determine the $\Delta$FEV1.0 time points that provided the best prediction of later development of NIPS. Time to relapse was calculated from time of transplantation to date of relapse or date of documented disease progression for patients never achieving complete remission. Overall survival was calculated from time of transplantation until death, with patients censored at last follow-up. For treatment-related mortality (TRM), patients were censored at last follow-up or at the time of relapse, because relapse was considered as a competing risk to TRM. Incidence of cGVHD and aGVHD were estimated by the cumulative incidence method and thus treated as time-dependent covariates [32]. Statistical analysis was performed using Stata version 12 (StataCorp LP, College Station, TX). Approval for this study was obtained from the Royal Melbourne Hospital institutional review board.

## RESULTS

Baseline characteristics of the 257 patients undergoing SCT are shown in Table 1. Spirometry testing was required per protocol to be within 2 weeks of D100, of 1 year, and of 2 years. One hundred seventy-five patients had a D100 FEV1.0, whereas 164 patients had their per-protocol 1-year FEV1.0.