Longitudinal Changes in Pulmonary Function Following Bone Marrow Transplantation*

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We prospectively followed a well characterized cohort of patients post-bone marrow transplantation for changes in pulmonary function. Thirty-four recipients without respiratory symptoms were available for follow up with a mean of two years. Spirometry and other measures of lung volume were well preserved following bone marrow transplantation. A progressive 11.9 percent decline in percent predicted diffusing capacity per year occurred. Age, cigarette smoking, type of cytoreductive therapy, type of GVHD prophylaxis, and the occurrence of AGVHD did not affect longitudinal changes in pulmonary function. Patients receiving transplants for CML developed a highly significant fall in diffusing capacity. Asymptomatic patients with CGVHD developed evidence of progressive obstructive ventilatory impairment. This suggests a subclinical spectrum of patients who may progress to the development of bronchiolitis obliterans and respiratory failure post-bone marrow transplantation.  

\[ \text{CML = chronic myelogenous leukemia; GVHD = graft-vs-host disease; AGVHD = acute graft-vs-host disease; CGVHD = chronic graft-vs-host disease; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AP = aplastic anemia; TBI = total body irradiation; CMV = cytomegalovirus; MHC = major histocompatibility complex} \]

Bone marrow transplantation offers patients with a variety of malignant and nonmalignant diseases the chance for potentially curative therapy. Long-term disease-free survival rates of 50 to 60 percent or better can now be achieved routinely in patients with acute nonlymphocytic leukemia in first remission as well as in patients with CML in the chronic or early accelerated phase. Although not as striking, long-term survival can be achieved in patients with ALL or patients who have failed chemotherapy.\(^{14}\) Broader application of marrow grafting in the treatment of nonmalignant disease, such as AP, genetic disorders of hematopoiesis, and immunodeficiency syndromes including AIDS, may become a reality.

Although survival after bone marrow transplantation is encouraging, the progressive development of pulmonary complications has become one of the most important factors limiting the overall success of marrow grafting. Nonbacterial interstitial pneumonia is a major complication of allogeneic bone marrow transplantation occurring in 30 to 40 percent of all patients and has a 60 percent mortality.\(^6\) Although most pulmonary complications occur within the first 100 days following marrow grafting, late pulmonary complications occur.\(^{6,7}\) Late pulmonary complications include infectious bronchopneumonia, progressive interstitial pneumonitis, and the development of chronic obstructive airway disease.\(^{8,9}\) Pulmonary function changes following bone marrow transplantation have revealed both restrictive and obstructive ventilatory defects.\(^{10-13}\)

In order to describe pulmonary functional changes following bone marrow transplantation and to determine clinical or demographic factors which might predict the development of pulmonary function abnormalities, we prospectively followed a well characterized cohort of patients posttransplantation for changes in pulmonary function. Factors influencing longitudinal changes in pulmonary function have been analyzed.

**Materials and Methods**

**Patient Population**

Beginning in January of 1983, patients undergoing bone marrow transplantation at the Johns Hopkins Hospital received complete pulmonary function tests prior to marrow grafting. All patients were requested to return six months, 12 months, and annually thereafter for follow-up testing. Transplant diagnoses were limited to ALL, AML, AP and CML for the purpose of this study. All patients more than 18 years old and in continuous hematologic remission with a minimum of six months' follow up are included in the present report. Forty patients who survived for at least six months were followed up elsewhere and are not included in the present report.

**Transplantation Procedures**

Patients with hematologic malignancies were generally treated
with a preparative regimen of busulfan plus cyclophosphamide or cyclophosphamide plus TBI as previously described. Both busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg) were given in divided doses during four days; TBI was given at 5 to 7.5 rads/min from a cobalt 60 source. All patients received 300 rads given daily for four consecutive days with lung shielding with six half-value layers on the third day. All patients with severe AP were treated with cyclophosphamide alone, as previously described. Graft-vs-host disease prophylaxis consisted of cyclosporine-A or steroids in combination with either cyclophosphamide or cyclosporine-A as previously described.

**Pulmonary Function Testing**

All patients received baseline pulmonary function studies approximately 14 days prior to bone marrow transplantation. Thereafter, follow-up pulmonary function studies were obtained at six months, 12 months and annually. Forced expiratory spirometry was performed in all patients with a Stead-Wells spirometer (Collins, Braintree, MA) according to standardized techniques. Lung volumes were measured by helium dilution technique and Dsb was performed. In the Dsb measurement, no correction was made for CO₂ absorption. The Dsb values were corrected for hemoglobin concentration by using the corrections of Cotes et al. Hemoglobin concentrations used for correction of Dsb were obtained on the same day as pulmonary function testing. Pulmonary function test results were expressed as absolute values as well as percent predicted values. Predicted values for pulmonary functions were those utilized in the pulmonary function laboratory at the Johns Hopkins Hospital.

**Data Analyses**

Initial and follow-up FEV₁, FVC, and Dsb tests were done for each patient at both the initial and final visits. Rate of change of a test was obtained by dividing the absolute change between the initial test value and the longest follow-up test result available by the interval between the tests and expressed as change per year. Rates of change of pulmonary function were compared for subgroups with different clinical and demographic characteristics including sex, smoking status, diagnosis, preparative drug regimen, AGVHD, CGVHD and GVHD prophylactic regimen. Statistical analysis was performed by use of Student’s t test and one-way analysis of variance.

**RESULTS**

**Demographic and Clinical Features**

The group consisted of 34 patients on whom serial pulmonary function testing was available. Five patients did not have technically adequate Dsb determinations at either baseline or follow up and were not included in the data analysis for this variable. Characteristics of the transplant recipients who were followed up elsewhere and our study population were compared. There were no significant differences in age at transplant, survival, sex, smoking status, diagnosis and preparative regimen. Nonstudy patients included a statistically significant (p = 0.03) excess of autologous transplants with a correspondingly significant difference in GVH prophylactic regimen.

The study population had a mean age of 27.5 years. The oldest patient studied was 50 years of age. Average follow up time was approximately two years, with a mean of 630.9 (SD, 629; range, 190 to 1,136) days.

**Table 1—Effect of GVHD Prophylactic Regimen: Rate of Change per Year (Percent Predicted)***

<table>
<thead>
<tr>
<th>GVHD Prophylaxis</th>
<th>No.</th>
<th>FEV₁</th>
<th>FVC</th>
<th>Dsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine-A</td>
<td>19</td>
<td>4.2±14.7</td>
<td>1.8±12.3</td>
<td>-10.4±24.4</td>
</tr>
<tr>
<td>(n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A,</td>
<td>5</td>
<td>-2.6±14.0</td>
<td>4.6±18.6</td>
<td>-35.9±15.0</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>(n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A,</td>
<td>8</td>
<td>0.2±4.6</td>
<td>1.4±4.3</td>
<td>-0.3±5.8</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>(n=7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>-2.3±16.6</td>
<td>9.4±19.6</td>
<td>-17.6±0.0</td>
</tr>
<tr>
<td>(n=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All values for lung function tests are given as mean ± SD.

There were 20 male and 14 female patients in the study cohort. Twenty-one patients had never smoked, eight patients were current cigarette smokers, and five were former smokers. The diagnostic groups for which patients underwent bone marrow transplantation included hematologic malignancies as well as AP. There were eight patients with a diagnosis of ALL, eight with AML, 14 with CML and four with AP. Thirty-two patients had allogeneic bone marrow transplantation and two patients had autologous transplants. The regimen to prepare patients for marrow grafting was a combination of busulfan and cyclophosphamide in seven patients, all of whom had AML. Twenty-three patients received TBI in combination with cyclophosphamide. This group included patients with ALL as well as CML. Four patients with AP received cyclophosphamide alone. The majority of patients received cyclosporine-A alone as GVHD prophylaxis, with smaller numbers of patients receiving cyclosporine-A in combination with cyclophosphamide and/or methylprednisolone. Two patients who had autologous transplants (Table 1) received no GVHD prophylaxis.

Of the 34 patients studied, eight developed AGVHD which in seven was graded in severity as grade 1 on a scale of 0 to 4. A single patient had AGVHD of grade 2 severity. Two patients developed interstitial pneumonitis, one appearing at 101 days posttransplantation and thought to be secondary to CMV and the second at 161 days posttransplantation of unknown origin. Nine patients developed CGVHD, with 25 being free of the disorder.

**Overall Changes in Pulmonary Function**

Baseline pulmonary function studies for the entire group are shown in Table 2. These results are most notable for the excellent pulmonary function in the patient population prior to transplantation. Mean percent predicted FEV₁ was 91.6 percent with a mean percent predicted FVC of 94.9 percent. When corrected for hemoglobin, percent predicted Dsb averaged 83.7 percent for the entire population.
Table 2—Baseline Pulmonary Function Prior to Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>Test</th>
<th>No.</th>
<th>Absolute Value (Mean ± SD)</th>
<th>Percent Predicted (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>34</td>
<td>4.32 ± 1.25 (L)</td>
<td>94.9 ± 14.5 (%)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>34</td>
<td>3.58 ± 0.93 (L)</td>
<td>91.6 ± 12.3 (%)</td>
</tr>
<tr>
<td>Dsb</td>
<td>32</td>
<td>25.1 ± 7.58 (ml/m/mm Hg)</td>
<td>83.7 ± 17.7 (%)</td>
</tr>
</tbody>
</table>

Longitudinal changes in pulmonary function are shown in Figure 1 for the entire group. Follow-up spirometric values were available in all 34 patients, but there were five patients without complete Dsb data. Thirty-two patients had baseline diffusion studies, but adequate follow-up studies were available in only 29. Mean rates of change of spirometric values were rather small, averaging 2.1 percent for percent predicted FEV₁ and 2.6 percent for percent predicted FVC per year. The Dsb fell more rapidly, 1.57 ml/m/mm Hg or 11.9 percent predicted per year.

Effect of Pre-bone Marrow Transplant Diagnosis

The effect of pre-bone marrow transplant diagnosis on longitudinal changes in pulmonary function is shown in Table 3. Follow-up spirometry revealed small changes in percent predicted FEV₁ and FVC for all diagnostic groups longitudinally following bone marrow transplantation. Analysis of variance failed to reveal any significant difference between the rate of change in spirometric values among the various disease groups. The patients with CML had a marked loss in Dsb with an average loss of 27 percent predicted Dsb over a year's time. This value was highly significant with a probability of <0.001 in contrast to the rates of change observed for patients with ALL, AML and AP.

Table 3—Effect of Pre-bone Marrow Transplant Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>FEV₁</th>
<th>FVC</th>
<th>Dsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>8</td>
<td>-3.06 ± 4.4</td>
<td>-1.19 ± 3.8</td>
<td>-3.90 ± 12.6</td>
</tr>
<tr>
<td>AML</td>
<td>8</td>
<td>+7.97 ± 19.8</td>
<td>+3.05 ± 11.8</td>
<td>-6.54 ± 16.8</td>
</tr>
<tr>
<td>AP</td>
<td>4</td>
<td>5.01 ± 7.6</td>
<td>-2.72 ± 13.7</td>
<td>18.66 ± 30.6</td>
</tr>
<tr>
<td>CML</td>
<td>14</td>
<td>0.94 ± 11.1</td>
<td>6.06 ± 23.0</td>
<td>-27.48 ± 18.6</td>
</tr>
</tbody>
</table>

p value | NS | NS | <0.001 |

Effect of Preparative Regimen

Similar results were obtained in regard to the effect of regimen used to prepare patients for transplantation (Table 4). No significant differences were noted on followup spirometry in patients who had received cyclophosphamide plus busulfan, TBI and cyclophosphamide, or cyclophosphamide alone. In terms of gas diffusion, patients receiving cyclophosphamide plus busulfan and patients receiving TBI plus cyclophosphamide had a mean loss of pulmonary function of 4.6 and 19.2 percent per year, respectively. In contrast, patients receiving cyclophosphamide only had a 15.7 percent yearly gain in percent predicted hemoglobin corrected Dsb (p <0.005). All patients who received cyclophosphamide only had a diagnosis of AP and thus received less intensive cytoreductive therapy than other patient groups. Comparison of patient groups receiving cyclophosphamide plus busulfan vs TBI plus cyclophosphamide in terms of rate of change per year percent predicted Dsb corrected was not significantly different.

![Figure 1. Mean rate of change per year in pulmonary function following bone marrow transplantation for the entire study population (mean + SD). N = 34 for FEV₁, percent predicted FEV₁, FVC; N = 29 for AVL, Dsb, percent predicted Dsb. AVL = alveolar volume; PP = percent predicted.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21598/)
Table 4—Effect of Preparative Regimen: Rate of Change per Year (Percent Predicted)*

<table>
<thead>
<tr>
<th>Preparative Regimen</th>
<th>No.</th>
<th>FEV₁</th>
<th>FVC</th>
<th>Dsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide, 7</td>
<td>9.7 ± 21.0</td>
<td>4.1 ± 12.5</td>
<td>-4.6 ± 15.6</td>
<td></td>
</tr>
<tr>
<td>Busulfan (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide, 23</td>
<td>-0.5 ± 9.5</td>
<td>3.2 ± 12.1</td>
<td>-19.2 ± 17.9</td>
<td></td>
</tr>
<tr>
<td>TBI (n = 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide, 4</td>
<td>3.1 ± 7.8</td>
<td>-2.5 ± 11.9</td>
<td>15.7 ± 22.5</td>
<td></td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

*All values for lung function tests are given as mean ± SD.

Effect of GVHD

There was no effect of AGVHD on changes in pulmonary function. In contrast, CGVHD was associated with a mean loss of 4.45 percent predicted FEV₁ per year. Patients without CGVHD had a mean gain of 4.3 percent predicted FEV₁ per year (p = 0.02) (Table 5). There was no significant difference in rate of change per year of percent predicted FVC or Dsb. Patients with CGVHD had a yearly rate of loss of FEV₁ of 116 m³/year in contrast to patients without CGVHD who had a net gain of 92 m³/year of FEV₁ (p = 0.10). Patients with and without CGVHD had a yearly gain of FVC of 6 and 165 m³/year, respectively. Progressive loss of FEV₁, with stable FVC is consistent with the development of airway obstruction in association with CGVHD.

Effect of GVHD Prophylactic Regimen

Several prophylactic regimens were used to prevent the development of GVHD in this cohort. The majority of patients received cyclosporine-A alone or in combination with cyclophosphamide or methylprednisolone. There were no significant differences among various prophylactic regimens in the rate of change of lung function (Table 4) when expressed as percent predicted (ie, adjusted for age, height and sex).

Discussion

The most important results of this study were the well preserved spirometric values in our patient population following bone marrow transplantation. There was, however, a progressive fall in Dsb averaging 11.9 percent per year. This population consisted largely of young patients without previous pulmonary disease and normal baseline pulmonary function. There was considerable variability and evidence of greater loss of pulmonary function among certain identifiable subpopulations of patients following bone marrow transplantation. Patients with a pre-bone marrow transplant diagnosis of CML showed the development of a gas transfer defect following marrow transplantation as indicated by the falling percent predicted Dsb of 27.5 percent per year. The significantly greater loss in Dsb in patients with CML cannot be attributed to greater cytotoxic therapy prior to bone marrow transplantation since in general CML patients received only oral hydroxyurea or busulfan in modest doses compared with patients with acute leukemia who received very high doses of chemotherapy. Also, unlikely is a synergistic action of prior busulfan exposure with cyclophosphamide and TBI given at the time of transplant. Only six of 14 patients with CML received busulfan and cyclophosphamide as a preparative regimen. Radiation sensitization by busulfan and synergy between busulfan and other alkylating agents have been described in anecdotal reports only. Why patients with CML were more susceptible to a fall in Dsb is unclear. Other indicators of toxicity such as venoocclusive disease of the liver and interstitial pneumonia are not more prevalent in patients with CML. Age cannot be used to account for these findings in CML patients. The mean age of patients with CML (28.5 years; range, 18 to 44 years) was comparable to those with other diagnoses (27 years; range, 18 to 55 years). Further study is needed to determine the etiology of the progressive fall in Dsb seen in patients with CML.

Analysis of the effect of preparative regimen on rate of change of pulmonary function was most significant for the fact that patients who received cyclophosphamide alone showed a 15.7 percent increase in mean percent predicted Dsb. This result might be accounted for by the less intensive bone marrow transplantation preparative regimen and also possibly the fact that all four patients receiving cyclophosphamide alone had a pretransplant diagnosis of AP and thus had received no exposure to chemotherapeutic agents prior to transplantation. There was no significant difference in rate of change of pulmonary function between patients receiving cyclophosphamide and busulfan vs those receiving TBI and cyclophosphamide.

CGVHD predisposed patients to the development of a progressive obstructive ventilatory defect. The development of CGVHD was associated with a mean
loss of 4.4 percent in percent predicted FEV$_1$ per year, in contrast to patients without GVHD who had a net gain in percent FEV$_1$ predicted of 4.3 percent. There were no significant differences in change in percent predicted FVC. In both the presence and absence of CGVHD, there was an associated loss of percent predicted Dsb of 13.5 and 11.2 percent per year, respectively. These were not significantly different. This is in keeping with the well described association of obstructive airway disease with CGVHD in multiple case reports. In the literature, the majority of these patients presented with progressive, severe and refractory dyspnea rapidly leading to deterioration and death due to respiratory failure. Postmortem examinations typically revealed evidence of bronchiolitis obliterans.

It is of note that our patient population was not selected on the basis of respiratory symptomatology. Clinical evaluation on the day of follow-up pulmonary function testing did not reveal significant signs or symptoms of respiratory disease in this population. Our data indicate that CGVHD is associated with the development of progressive airflow obstruction which often is asymptomatic. None of the patients in the present study developed symptomatic or rapidly progressive bronchiolitis obliterans. Obstructive ventilatory defects following marrow transplantation may be more prevalent than previously suspected, since CGVHD ultimately occurs in approximately 30 percent of patients posttransplantation. It also may be possible to detect early manifestations of CGVHD by serial lung function testing.

The origin of progressive airflow obstruction following bone marrow transplantation remains obscure. Similar long-term pulmonary complications have been described following combined heart-lung transplantation. In these patient populations, the development of obliterative bronchiolitis has been thought to be a manifestation of isolated lung rejection and/or viral infection. The fact that obliterative bronchiolitis has not been described as a complication of renal, hepatic and other organ transplantation requiring similarly intense immunosuppression suggests that obliterative bronchiolitis may be a unique manifestation of lung graft rejection or CGVHD within the lung. Support for this concept comes from the fact that class 2 MHC antigens are known to be expressed on human vascular endothelium and immune inflammation (immune interferon and activated T cells) appears to increase the level of expression. Similar induction of class 2 MHC antigen expression has been shown for various tissue epithelial cells, including lung epithelial cells, at sites of cellular inflammation. Bronchial epithelium may be a cellular target for CGVHD within the lung. Since loss of epithelial integrity after inflammatory damage has been implicated in the development of bronchial hyperresponsiveness, it would be of interest to test asymptomatic marrow recipients with evidence of airway obstruction for potential reversibility.

The results of the present study differ somewhat from those that have been reported previously. Springmeyer et al prospectively evaluated pulmonary function in a large group of marrow transplant patients returning at yearly intervals and noted the development of mild restrictive ventilatory changes. Pulmonary function changes within the population as a whole were examined but a well-defined cohort was not available for longitudinal study. In the current study, our patient population had excellent baseline pulmonary function with a tendency toward preservation of lung function with a mean of two years of followup. For the population as a whole, there was a progressive decline in Dsb most marked in patients with a diagnosis of CML. In the study cited previously, airflow obstruction appeared with increasing frequency in patients followed up at one, two and three years post-bone marrow transplantation. In contrast to the present study, that study did not find an association of progressive airway obstruction with CGVHD. In more recent work from the same authors, CGVHD was identified as an important risk factor for the development of airflow obstruction at one year post-marrow transplantation. The combined use of methotrexate and the occurrence of CGVHD was strongly associated with decreases in FEV/FVC ratio at one year of followup. Methotrexate was not utilized as a GVHD prophylactic regimen in our patients. Sorensen et al observed a progressive decline in Dsb and VC in a group of patients with leukemia followed up for one year post-marrow transplantation. They attributed these changes to the use of TBI as a primary preparative regimen for transplantation. Similar changes were noted by Depledge et al in AML patients treated with TBI and marrow grafting. In the present study, we found the greatest decline in percent predicted Dsb in patients receiving TBI in combination with cyclophosphamide although the decline was not of statistical significance compared with that of patients receiving cyclophosphamide and busulfan. The use of cyclophosphamide alone actually showed a net preservation of lung function with a mean of two years of follow up.

In conclusion, follow-up pulmonary function studies in a well characterized cohort of patients post-bone marrow transplantation revealed well preserved spirometry and lung volumes at a mean of two years of follow up. Progressive decline in Dsb was noted especially in patients with a diagnosis of CML. No significant difference was noted in the preparative regimen of busulfan and cyclophosphamide vs TBI and cyclophosphamide, although there was a tendency for the latter to show a greater loss of Dsb with time.
The development of CGVHD was associated with a progressive loss of FEV₁ and stable FVC suggesting progressive airway obstruction. We speculate that an asymptomatic group of patients with CGVHD may represent a subclinical spectrum of patients who may progress to the development of interstitial pneumonitis and obstructive airway disease post-bone marrow transplantation.

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References