Diffuse Pulmonary Infiltrates After Bone Marrow Transplantation: The Role of Open Lung Biopsy

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Background. Diffuse pulmonary infiltrates is the major complication and cause of mortality after bone marrow transplantation. We analyzed the etiologies and prognostic factors in bone marrow recipients with diffuse pulmonary infiltrates and assessed the role of open lung biopsy in managing this complication.

Methods. Medical records of patients with diffuse pulmonary infiltrates after bone marrow transplantation were reviewed. Possible prognostic factors were analyzed by multivariate logistic regression.

Results. Sixty-eight (20%) of 341 bone marrow recipients had diffuse pulmonary infiltrates and 34 died. Thirty-five underwent open lung biopsy, resulting in therapeutic changes in 22 (63%) and clinical improvement in 16 (46%). The leading diagnoses were idiopathic interstitial pneumonitis (40%) and cytomegalovirus pneumonitis (20%). Cytomegalovirus pneumonitis caused radiographically observable interstitial infiltrates exclusively and was frequently associated with hepatitis. Idiopathic interstitial pneumonitis resulted in either diffuse ground-glass opacity or interstitial infiltrates. Three (9%) patients had miliary tuberculosis. Respiratory failure (p < 0.001) and acute graft-versus-host disease (p = 0.016) were the poor prognostic factors.

Conclusions. Among bone marrow recipients, we found diffuse pulmonary infiltrates in 20% and a mortality rate of 50%. Idiopathic interstitial pneumonitis and cytomegalovirus pneumonitis were the most common causes and should be suspected in patients with diffuse interstitial infiltrates. In endemic areas, miliary tuberculosis should be suspected in bone marrow recipients with diffuse reticulonodular lesions. Respiratory failure and acute graft-versus-host disease were poor prognostic factors. By establishing a correct diagnosis, open lung biopsy led to treatment changes in about two-thirds of these patients.

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Patients and Methods

This study was conducted in the National Taiwan University Hospital, a tertiary-care referral center with 2,000 beds, by review of the medical records and chest images of 341 patients with hematologic diseases who underwent BMT between July 1995 and June 2001. Patients in whom DPI developed were included, with DPI defined as the presence of infiltrates over all four quadrants of the lung fields as seen on chest radiograph. The date of onset was defined as the earliest date when image study demonstrated DPI. All chest images were reviewed by 1 radiologist and 1 chest specialist. If discrepancies were noted between their interpretations, the image was further reviewed by 1 chest specialist blinded to the results. Patients in whom DPI developed after septic shock or at the terminal stage of other diseases were excluded from this study. Prophylactic ganciclovir against cytomegalovirus (CMV) for allogeneic recipients and trimethoprim-sulfamethoxazole against Pneumocystis carinii for all recipients were prescribed during transplantation if a patient’s leukocyte count was higher than 2,000 k/μL and platelet count above 50 k/μL. All allogeneic bone marrow recipients received cyclosporin-containing regimens for preventing graft-versus-host disease (GVHD).

Once DPI developed, computed tomography of the chest, bacteriology studies, serology tests for Mycoplasma
and Chlamydia, antigen assays for Legionella and Cryptococcus, microscopic examination of sputum for Pneumocystis carinii and assays for CMV antigenemia or viremia were performed. Patients underwent open lung biopsy when diagnosis was not reached by the above-mentioned studies (early biopsy). Alternatively, if the patient's condition did not improve within 3 days with empirical therapy, open lung biopsy was then arranged (late biopsy). Bronchoscopy, including transbronchial biopsy and bronchoalveolar lavage, was performed if the patient was too weak to undergo general anesthesia or refused open lung biopsy. In truly diffuse processes, the lingula biopsy was taken from the most involved area. The biopsy was performed by video-assisted thoracoscopy if the patient could tolerate single-lung ventilation, otherwise by minithoracotomy. All biopsy specimens were reviewed by 2 pulmonary pathologists.

Therapeutic changes included use, discontinuation, or change of antimicrobial or immunosuppressive agents. The response of the treatment specified to the pathologic diagnosis was assessed according to the patient's symptoms and laboratory and radiographic findings as assessed by primary care physicians, including a specialist in BMT and a specialist in critical care.

Cytomegalovirus pneumonitis was diagnosed if the histologic examination showed interstitial pneumonitis characterized by intranuclear or cytoplasmic inclusion bodies with confirmed immunohistochemical CMV antibody stain, or a positive CMV culture from the lung biopsy specimen [12]. Active CMV infection was diagnosed by positive CMV antigenemia [13] or viremia [14], or CMV pneumonitis. Idiopathic interstitial pneumonitis (IIP) was diagnosed if the histologic examination revealed diffuse interstitial pneumonitis with some cases resembling diffuse alveolar damage or nonspecific interstitial pneumonia in the absence of an identifiable infectious agent [15].

Statistical Analysis
Variables with possible survival impact were analyzed. The variables included age at transplantation, sex, underlying hematologic disease and remission status while undergoing BMT, smoking, pulmonary function before BMT, type of BMT (autologous or allogeneic), conditioning regimens [16], timing of the onset of DPI (more than 100 days or 100 or fewer days after BMT), initial multiple organ dysfunction score (MODS) [17], respiratory failure, acute GVHD, and open lung biopsy. Respiratory failure was defined as partial pressure of arterial oxygen (Pao2) of less than 60 mm Hg or partial pressure of arterial carbon dioxide (Paco2) of more than 50 mm Hg while breathing room air, or requiring assisted ventilation [18]. The diagnosis, grading, and treatment of GVHD were determined as reported previously [19].

Logistical regression was applied to identify factors independently associated with mortality. Variables were entered into the multivariate analysis if a significant difference (p < 0.05) was obtained in the univariate analysis. Intergroup differences were analyzed using either the independent-samples t test (continuous variables) or χ² test (categorical variables).

Results
From July 1995 through June 2001, pulmonary infiltrates after BMT occurred in 188 (55.1%) of 341 patients. Diffuse pulmonary infiltrates developed in 68 (19.9%) of the 341 patients, including 63 (23.7%) of 266 allogeneic recipients and 5 (6.67%) of 75 autologous recipients. The clinical characteristics of the 68 patients are listed in Table 1. Relapse of underlying disease before the onset of DPI was proved in 5 (7.4%) of the 68 patients. Sputum collected during the course of DPI was cytologically free of malignant cells. Nineteen patients underwent early biopsy and 16 underwent late biopsy. The median interval between BMT and open lung biopsy was 137 days (range 17 to 925 days). At the time of lung biopsy, 10 patients required ventilator support and 7 patients had ratios of Pao2/Fio2 (fractional concentration of inspiratory oxygen) of more than 300.

The pathologic diagnoses of the 35 patients who underwent biopsy and their radiographic findings are listed in Table 2. Major discordance between clinical and pathologic diagnoses was noted in 22 (62.9%) patients, including 12 early and 10 late biopsy patients. The results of open lung biopsy led to therapeutic change in 22 (62.9%) patients. Ten early biopsy patients and 6 late biopsy patients responded to the altered treatment in their clinical symptoms and pulmonary infiltrates (χ² test, p = 0.500). One other late biopsy patient had transient improvement.

Thirty-four (50.0%) of the 68 patients with DPI died, 33 before undergoing biopsy. The cause of death was respiratory failure in 30 (88.2%), brain abscess resulting in fatal brain herniation in 2 (5.88%), and septic shock in 1 (2.94%). Of the 35 patients undergoing biopsy, 1 (2.9%) patient died of massive hemothorax after minithoracotomy refractory to reoperation. The surgical morbidity among the 35 patients undergoing biopsy (n = 2; 5.7%) included transient wound dehiscence in 1 patient and bleeding that required blood transfusion in another patient. In the 35 biopsy patients, we noted 11 episodes of adverse drug reaction (31.4%), including four cases of
neutropenia (neutrophil counts < 1,000 k/μL on 2 consecutive days), five of renal dysfunction, and two of hepatic dysfunction. However, among the 33 patients without open lung biopsy we noted 18 episodes (54.5%) of adverse drug reaction, including nine cases of neutropenia, seven of renal dysfunction, and two of hepatic dysfunction (χ² test, p = 0.054).

Four (57.1%) of the 7 CMV pneumonitis patients had abnormal liver function on admission, compared with none of the IIP patients. The onset of DPI in CMV pneumonitis patients was earlier than that among IIP patients (64 ± 48 days compared with 115 ± 93 days). Respiratory failure developed in 5 of the 7 CMV pneumonitis patients and all 5 died, whereas 2 of the 14 patients with IIP died (mortality 71.4% compared with 14.3%). Of the 35 patients who received open lung biopsy, tuberculosis caused DPI in 3 (8.6%) patients with the onset at 124, 584, and 605 days after BMT, respectively. Tuberculosis was also the most common etiology of radiographically diffuse reticulonodular infiltrates (Table 2). *Mycobacterium tuberculosis* was isolated from the biopsy specimens of all 3 patients. The last patient also had tuberculous hepatitis proved by liver biopsy. Additionally, all 3 of these patients had GVHD.

Bronchoscopy was performed in 13 patients, 7 of whom had the procedure before open lung biopsy. Among these 7, bronchoscopy was nondiagnostic in 4. Of the 4 patients, the open lung biopsy revealed IIP in 2, pulmonary tuberculosis in 1, and CMV pneumonitis in the other. Among the 3 for whom bronchoscopy was diagnostic, the bronchoscopic diagnosis was compatible with the result of open lung biopsy in 2 patients with IIP. The bronchoscopy revealed pulmonary candidiasis in the other patient, whose open lung biopsy showed lymphoma relapse. Six patients who did not receive open lung biopsy underwent bronchoscopy, in which 5 were nondiagnostic and the other had a diagnosis of pulmonary aspergillosis. Five (38.5%) of the 13 patients received therapeutic changes after bronchoscopy.

Table 3 shows the intubation rate and the number of days on a ventilator in the 6 patients who received only bronchoscopy and the 35 patients who underwent open lung biopsy. The clinical diagnostic categories and outcome of the 33 patients who did not receive open lung biopsy were listed in Table 4.

In the univariate analysis, factors significantly associated with outcome (survival or death at discharge) were respiratory failure, acute GVHD, and open lung biopsy. Respiratory failure and acute GVHD were independently associated with mortality in the multivariate analysis (Table 5). Respiratory failure developed in 44 patients with a mean time of 14 days after the onset of respiratory symptoms (range 0 to 107 days). Of them, 19 underwent open lung biopsy. The most common pathologic diagnoses were CMV pneumonitis (5 patients, 26.3%) and IIP (5 patients, 26.3%), with mortality rates of 100% and 0%, respectively. In patients with acute GVHD, the mean interval between BMT and the onset of DPI was 111 days, whereas the mean interval in patients without acute GVHD was 255 days. Of the 39 patients with acute GVHD, active CMV infection was diagnosed in 16 (41%), of whom 13 (81.3%) died. However, only 1 of the 29 patients without acute GVHD had active CMV infection.

**Comment**

Consistent with previous reports [2, 3], our incidence of pulmonary infiltrates after BMT was 55.1% (188 of 341 patients). About one-third of these patients had DPI (68
of 188 patients; 36.2%), with a high mortality rate (50%). The results of open lung biopsy caused major therapeutic change in two-thirds and were associated with clinical improvement in nearly half of the biopsy patients. Patients who underwent open lung biopsy had a much shorter length of mechanical ventilation than patients who underwent only bronchoscopy. The most common pathologic diagnoses were IIP and CMV pneumonitis. Idiopathic interstitial pneumonitis had a much lower mortality rate. All of the CMV pneumonitis patients with respiratory failure died. Cytomegalovirus pneumonitis presented with radiographically confirmed interstitial pulmonary infiltrates exclusively, whereas IIP caused either interstitial infiltrates or diffuse ground-glass opacity. Tuberculosis was the most common etiology of diffuse pulmonary infiltrates, and we excluded patients in whom DPI developed after septic shock. These criteria may have excluded most patients with bacterial or fungal pneumonia. In addition, the incidence of infectious complication after transplantation may have been largely reduced by preemptive therapy for CMV disease and trimethoprim-sulfamethoxazole prophylaxis [29–31]. Thus the overall diagnostic rate of bronchoscopy among our BMT patients with pulmonary infiltrates was reduced. Second, fiber optic bronchoscopy is performed under local anesthesia rather than general anesthesia in our hospital, thus greatly increasing the technical difficulty in sampling.

Open lung biopsy is the gold standard for the diagnosis of pulmonary disease in BMT patients [3–7]. As in previous reports [11, 32], open lung biopsy failed to demonstrate a survival benefit in our study (Table 3). However, nearly two-thirds of the clinical diagnoses were wrong and uncertain, leading to the administration of many unnecessary drugs to cover all possible etiologies of DPI and subsequently increasing drug-related toxicities and costs of treatment. Although the intubation rates were similar, the duration of mechanical ventilation was much

### Table 2. Disease Mortality and Correlation Between Pathologic Diagnoses and Radiographic Findings of the 35 Patients Receiving Open Lung Biopsy

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Number of Cases</th>
<th>Intubation, n (%)</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious etiology</td>
<td>12/35 (34.3%)</td>
<td>6 (50.0%)</td>
<td>72.7</td>
</tr>
<tr>
<td>CMV pneumonitis</td>
<td>7</td>
<td>5 (71.4%)</td>
<td>72.7</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3</td>
<td>1 (33.39%)</td>
<td>72.7</td>
</tr>
<tr>
<td>PCP</td>
<td>1</td>
<td>0</td>
<td>72.7</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>1</td>
<td>0</td>
<td>72.7</td>
</tr>
<tr>
<td>Noninfectious etiology</td>
<td>23/35 (65.7%)</td>
<td>7 (30.4%)</td>
<td>72.7</td>
</tr>
<tr>
<td>IIP</td>
<td>14</td>
<td>2 (14.3%)</td>
<td>72.7</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>5</td>
<td>1 (20.0%)</td>
<td>72.7</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>1</td>
<td>1 (100%)</td>
<td>72.7</td>
</tr>
<tr>
<td>Capillaritis</td>
<td>1</td>
<td>1 (100%)</td>
<td>72.7</td>
</tr>
<tr>
<td>Lymphoma relapse</td>
<td>1</td>
<td>1 (100%)</td>
<td>72.7</td>
</tr>
<tr>
<td>PTLD</td>
<td>1</td>
<td>1 (100%)</td>
<td>72.7</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; IIP = idiopathic interstitial pneumonitis; PCP = Pneumocystis carinii pneumonia; PTLD = post-transplant lymphoproliferative disorder.

These findings may have two reasons. First, our percentage of infection-related DPI (36.2%) was lower than previous studies (50% to 73%) [15, 28], probably because we included only patients with DPI, not localized infiltrates, and we excluded patients in whom DPI developed after septic shock. These criteria may have excluded most patients with bacterial or fungal pneumonia. In addition, the incidence of infectious complication after transplantation may have been largely reduced by preemptive therapy for CMV disease and trimethoprim-sulfamethoxazole prophylaxis [29–31]. Thus the overall diagnostic rate of bronchoscopy among our BMT patients with pulmonary infiltrates was reduced. Second, fiber optic bronchoscopy is performed under local anesthesia rather than general anesthesia in our hospital, thus greatly increasing the technical difficulty in sampling.

### Table 3. Intubation Rates and Ventilator Days

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Number of Cases</th>
<th>Intubation, n (%)</th>
<th>Ventilator Days (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy only</td>
<td>6</td>
<td>3 (50.0%)</td>
<td>36.0</td>
</tr>
<tr>
<td>Open lung biopsy</td>
<td>35</td>
<td>20 (57.1)</td>
<td>13.7</td>
</tr>
</tbody>
</table>

### Table 4. Clinical Diagnosis and Outcome of 33 Patients Without Open Lung Biopsy

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Expired (n)</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious pneumonitis</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Inflammatory pneumonitis</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>
shorter for patients who underwent open lung biopsy than that for patients who underwent only bronchoscopy. Although bleeding tendency and poor pulmonary reserve might be concerns, open lung biopsy, either performed by mini-thoracotomy or video-assisted thoracoscopy, is safe with a surgical mortality rate of less than 3%.

The most common pathologic diagnoses were IIP and CMV pneumonitis, which were also the leading causes of radiographically confirmed interstitial infiltrates. However, the mortality rate of infectious pneumonitis, especially CMV pneumonitis, was much higher than that of inflammatory pneumonitis (Tables 2 and 4). Most BMT patients with diffuse pulmonary ground-glass opacity also had IIP. Our results suggest that CMV pneumonitis is more common than IIP in patients with diffuse interstitial pulmonary infiltrates and concomitant hepatitis [33] shortly after BMT.

Miliary tuberculosis, which was rarely reported as the cause of DPI after BMT, was the fourth leading cause in our study, probably reflecting the high incidence of tuberculosis among the general population in Taiwan [34]. It was also the most common disease causing diffuse reticulonodular infiltrates on chest radiographs. GVHD seemed to be the precipitating factor. Thus, in endemic areas, there should be a strong index of suspicion for miliary tuberculosis in BMT patients with GVHD and diffuse reticulonodular pulmonary infiltrates.

In our study, the variables that were independently associated with outcome were respiratory failure and acute GVHD. Severe lung damage leading to respiratory failure has been noted as the most common cause of death in BMT patients [9, 10, 20, 21, 35]. The mortality is even higher in patients with CMV pneumonitis and respiratory failure (100% in our study) [36]. Although the response rates in our study were not statistically different between the early biopsy group and the late biopsy group, these findings suggest that if the patient’s pulmonary condition continues to deteriorate and a pathologic diagnosis is desired, open lung biopsy should be performed before respiratory failure develops in BMT patients with DPI.

Acute GVHD has been shown to increase mortality, especially infection-related mortality, in BMT patients [37]. In our study, the mortality rate doubled and the onset of DPI was significantly earlier if acute GVHD developed. Acute GVHD and active CMV infections were also highly correlated, probably because the immunosuppression associated with GVHD precipitates opportunistic infections [37]. Conversely, CMV may also initiate and enhance the development of GVHD [38, 39].

Our study has some limitations. First, the criteria for open lung biopsy were not clearly defined. Although the MODS at the onset of DPI were not statistically different between the biopsy and nonbiopsy groups, open lung biopsy might still be inappropriate as a prognostic factor because of the possible selection bias that the decision to proceed to open lung biopsy was related specifically to the severity and extent of disease. Second, the treatment protocols were devised by the primary care physicians and were not standardized. Third, the causes of death in the 34 patients were not known because no autopsy was performed. In addition, our patient group was too small to draw powerful conclusions. Further, large controlled studies are needed to evaluate the benefits, safety, and costs of open lung biopsy in patients with DPI after BMT.

In conclusion, 20% of BMT patients developed DPI with a mortality rate of 50%. The mortality rate was even higher among patients with respiratory failure or acute GVHD. By providing a definite diagnosis by open lung biopsy early before the onset of respiratory failure, treatment could become more specific, thus reducing the drug-related complications and probably shortening the length of mechanical ventilation and improving the outcome. Idiopathic interstitial pneumonitis and CMV pneumonitis accounted for 60% of the etiologies of DPI and were also the most common cause of radiographically confirmed interstitial pulmonary infiltrates. But CMV pneumonitis is frequently associated with hepatitis and tends to occur shortly after BMT. Idiopathic interstitial pneumonitis should also be considered in those with diffuse ground-glass opacity. In areas endemic for tuberculosis, miliary tuberculosis should be highly suspected in BMT patients with GVHD and diffuse pulmonary reticulonodular lesions.

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**Table 5. Univariate and Multivariate Analysis of Prognostic Factors of Diffuse Pulmonary Infiltrates After BMT in 68 Patients**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mortality, n (%)</th>
<th>Univariate p</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>44</td>
<td>33 (75)</td>
<td>&lt; 0.001</td>
<td>60.35  (6.62 to 550.21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Not present</td>
<td>24</td>
<td>1 (4.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>25 (64.1)</td>
<td>0.006</td>
<td>6.26  (1.28 to 30.75)</td>
<td>0.016</td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>9 (31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open lung biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received</td>
<td>35</td>
<td>13 (37.1)</td>
<td>0.028</td>
<td>0.23  (0.05 to 1.11)</td>
<td>0.053</td>
</tr>
<tr>
<td>Not received</td>
<td>33</td>
<td>21 (63.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMT = bone marrow transplantation; CI = confidence interval; GVHD = graft-versus-host disease; OR = odds ratio.
References


