Empiric Prednisone Therapy for Pulmonary Toxic Reaction After High-Dose Chemotherapy Containing Carmustine (BCNU)*

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Study objective: To determine pretreatment factors that predict for pulmonary toxic reactions after high-dose chemotherapy containing carmustine (BCNU) and to determine the utility of prednisone in preventing pulmonary toxic reactions.

Design: Retrospective review.

Setting: Tertiary care referral center.

Patients: Forty-five patients with relapsed or refractory lymphoma and 27 patients with breast cancer with normal cardiopulmonary function were treated with one of two high-dose combination chemotherapeutic regimens containing the same dose of BCNU.

Measurements: Recorded pretreatment patient characteristics included previous chemotherapy or radiation therapy, history of pulmonary metastases, history of chronic obstructive pulmonary disease, and history of smoking. Spirometry and single-breath carbon monoxide diffusing capacity (Dco) were obtained before and after high-dose chemotherapy.

Interventions: Patients were treated with prednisone for a 5% or more drop in postchemotherapy Dco whether or not symptoms were present.

Results: Fifty-nine patients were evaluable. No pretreatment characteristic predicted for declines in pulmonary function postchemotherapy. The FEV1/FVC ratio did not change significantly after high-dose chemotherapy, but the Dco decreased 12.1% (p<0.001). Of the 59 evaluable patients, 30 were treated with prednisone for declines in postchemotherapy Dco. Sixteen (53%) of these 30 patients were asymptomatic. The Dco increased 10.3% in patients treated with prednisone compared with a decrease of 2.3% in patients not treated (p=0.017). There was no statistically significant difference in FEV1/FVC in patients treated with prednisone compared with those not treated. Regression analysis of pretreatment characteristics, type of high-dose chemotherapy received, and treatment with prednisone identified only treatment with prednisone as a significant variable in predicting an increase in Dco (p=0.03; regression coefficient=+11.5%, SE=±5.2%) after high-dose chemotherapy containing BCNU.

Conclusions: High-dose BCNU-containing chemotherapeutic regimens cause decreases in Dco that are often asymptomatic and likely represent subclinical pulmonary toxic reactions. Pretreatment clinical parameters cannot predict which patients will manifest pulmonary toxic reactions after high-dose chemotherapy. Empiric treatment with prednisone will reverse chemotherapy-induced decreases in Dco. Earlier institution of glucocorticoids for evidence of pulmonary dysfunction is recommended.

Key words: bone marrow transplant; carmustine; diffusing capacity; prednisone; pulmonary toxicity

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Manuscript received May 6, 1994; revision accepted June 17.

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BCNU = carmustine; BMT = bone marrow transplant; CBV = etoposide (VP-16) 2,400 mg/m² IV over 36 h d-8 to d-6; cyclophosphamide, 1,500 mg/m² IV over 2 h d-6 to d-3; BCNU, 600 mg/m² IV over 2 h d-2; CCB = cyclophosphamide, 1,575 mg/m² IV d-5 to d-3; cisplatin, 55 mg/m² IV d-5 to d-3; BCNU, 600 mg/m² IV over 2 h d-2; CMV = cytomegalovirus; Dco = single-breath carbon monoxide diffusing capacity; Dco/Va = Dco to alveolar volume ratio; FEV1/FVC = forced expiratory volume in 1 s to forced vital capacity ratio; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IV = intravenous; LP = leukocyte-poor; SE = standard error; VA-alveolar volume

Standard doses of several chemotherapeutic agents may cause pulmonary toxic reactions.1 One agent long recognized as a pulmonary toxin is carmustine (BCNU).5 The toxic reaction in the lung caused by BCNU usually manifests as chronic interstitial fibrosis that occurs after prolonged treatment and high cumulative doses.3,4 Pulmonary toxic reactions proved to be dose limiting in early studies using escalating doses of single-agent BCNU followed by autologous bone marrow transplant (BMT).5

Recently, BCNU has been incorporated into several combination high-dose chemotherapy regimens. As clinical experience with these regimens grows, pulmonary toxic reactions are being recognized more frequently in patients treated for breast cancer and lymphoma.6-8 Pulmonary toxic reactions occur in as many as 40% of patients treated with high-dose chemotherapy containing BCNU for breast cancer.9 The
toxic reaction manifests as cough, dyspnea, and commonly fever with or without associated interstitial pulmonary infiltrates. The diffusing capacity of the lung as measured by the single-breath carbon monoxide test (Dco) is usually decreased, reflecting interstitial lung damage typical of BCNU lung injury. The syndrome can be severe and potentially fatal but several reports suggest glucocorticoid treatment can result in improvement of symptoms and increased Dco.

Although some investigators have suggested age and previous chest radiotherapy to be risk factors for the subsequent development of pulmonary toxic reactions following treatment with high-dose chemotherapy, other studies have failed to confirm their prognostic value. Some studies suggest that declines in Dco predict subsequent clinically significant BCNU-induced lung injury, but ideally one would identify patients at risk and institute prophylactic measures to prevent this complication. We reviewed our data in autologous BMT using BCNU as part of the preparative regimen in an attempt to identify patients at risk for pulmonary toxic reactions. In addition, we retrospectively investigated the role of empirical prednisone therapy in prevention of severe pulmonary toxic reactions in patients who either demonstrate signs and symptoms of pulmonary toxic reactions or exhibit an asymptomatic decrease in Dco after treatment with high-dose chemotherapy containing BCNU.

**METHODS AND MATERIALS**

**Patient Selection**

Pulmonary toxic reactions were assessed in two groups of patients undergoing autologous BMT using BCNU as part of the preparative regimen at the Cleveland Clinic Foundation. Forty-five consecutive patients with relapsed or refractory lymphoma and 27 consecutive patients with breast cancer treated from November 1, 1991 to November 23, 1992 were reviewed. All patients were required to have normal cardiac (left ventricular ejection fraction >50%), pulmonary (Dco >50% predicted), renal (serum creatinine <2 mg/dL), and hepatic (liver function test results <1.5 times the upper limit of normal) function at the time of transplant. Patients with central nervous system disease or disease refractory to salvage chemotherapy were excluded. All patients were treated on protocols approved by the Institutional Review Board of the Cleveland Clinic Foundation after giving informed consent.

**Preparative Regimens**

All patients treated for a diagnosis of relapsed or refractory lymphoma were treated with the same preparative regimen. Etoposide (VP-16) 2,400 mg/m² was infused over 36 h followed by cyclophosphamide, 1,800 mg/m² infused daily over 2 h on 4 consecutive days. BCNU reconstituted with 1 mL absolute alcohol per 100 mg BCNU was then administered at a dose of 600 mg/m² over 2 h the next day. This regimen is known as "CBV.": Autologous cryopreserved, unpurged bone marrow, peripheral blood progenitor cells, or both were infused 48 h after the BCNU.

Granulocyte colony-stimulating factor (G-CSF), 16 μg/kg, or granulocyte macrophage colony-stimulating factor (GM-CSF) 250 μg/m², was administered daily until the absolute neutrophil count rose to either 10,000/μL or 5,000/μL on 2 consecutive days.

All patients treated for breast cancer received a different BCNU containing preparative regimen. Cyclophosphamide, 1,875 mg/m², was administered daily simultaneously with cisplatin, 55 mg/m², as a continuous infusion daily for 3 days. BCNU reconstituted with 3 mL/100 mg of BCNU was then administered at a dose of 600 mg/m² over 2 h. This regimen is known as "CCB.": Autologous cryopreserved, unpurged bone marrow, peripheral blood progenitor cells, or both were infused 48 h after the BCNU. G-CSF, 16 μg/kg intravenously (IV), was administered daily following the infusion of bone marrow until the absolute neutrophil count rose to either 10,000/μL or 5,000/μL on 2 consecutive days.

**Supportive Care**

All patients were managed in a dedicated BMT transplant unit. Standard infection control procedures were followed. All patients received antibiotic prophylaxis with ciprofloxacin, 500 mg orally twice daily, in addition to low-dose amphotericin B (0.1 mg/kg IV every day) and acyclovir, 250 mg/m² IV every day. Irradiated, cytomegalovirus (CMV) negative, leucocyte poor (LP) red blood cell transfusions were administered to maintain the hematocrit greater than 25% in the CBV group and greater than 45% in the CCB group. Irradiated, CMV negative, LP platelet transfusions were administered for platelet counts less than 20,000/μL or bleeding. Broad-spectrum antibiotic therapy was initiated for fever greater than 38°C and was continued until the granulocyte count was greater than 500/μL on 2 consecutive days. Full-dose amphotericin B therapy was started empirically after 48 h of persistent or recurrent fever despite antibiotic therapy.

Patients were discharged from the hospital when they were afebrile, transfusion independent, and had granulocyte counts greater than 1,000/μL.

**Measurements**

Recorded pretreatment patient characteristics included previous chemotherapy, previous chest radiotherapy therapy, history of chronic obstructive pulmonary disease, and history of smoking defined as greater than a 5 pack-year history. History of pulmonary metastases was also noted.

Pulmonary function tests, including spirometry and Dco, were obtained before and after transplant. Spirometry was performed on a spirometer (Spinnaker TL, Cybermed Inc, Louisville, Colo). The FVC, FEV₁, and FEV₁/FVC ratio were collected for each of three efforts. Reference equations for spirometry were those of Crapo and coworkers. The Dco was determined in a sitting position using an automated pulmonary function testing unit (Cybermedic), according to American Thoracic Society guidelines, by Ogilvie's method. Reference equations for Dco were those of Burrows et al. The Dco was adjusted for alveolar volume (VA), as well as a standard hemoglobin concentration of 14.6 g/dL by the technique of Cotes.

Chest radiographs were obtained weekly until hospital discharge and then at follow-up appointments in conjunction with pulmonary function testing. Additional pulmonary function tests were obtained at the discretion of the treating physician.

Patients were evaluated for signs or symptoms of pulmonary dysfunction from the time of their first pulmonary function test after high-dose chemotherapy. Symptoms included cough, dyspnea, and fever. Signs included tachypnea, tachycardia, fever, cracks or wheezes by auscultation, and evidence of interstitial pneumonitis by chest radiographs. If symptoms, signs, and a decline in Dco were noted simultaneously, pulmonary toxic reaction was diagnosed. Management of asymptomatic and symptomatic pulmonary dysfunction was at the discretion of the treating physician. When prescribed, prednisone was administered at doses

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Table 1—Characteristics of 59 Patients Treated With BCNU-Containing High-dose Chemotherapeutic Regimens

<table>
<thead>
<tr>
<th></th>
<th>CBV</th>
<th>CCB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>34</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>Average age, yr</td>
<td>43</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Smoking history,</td>
<td>12</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous radiotherapy,</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung metastases,</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistics

The change in FEV\textsubscript{1}/FVC, D\textsubscript{co}/VA, and the percent of predicted D\textsubscript{co} between baseline and posttreatment values were tested to be different from zero using a two-sided Wilcoxon signed rank test. Statistical analysis of the effects of treatment group and various prognostic factors like history of smoking, history of lung metastases, and previous chest radiotherapy on FEV\textsubscript{1}/FVC and D\textsubscript{co} was performed. The two-tailed Fisher’s exact test was used to compare the treatment groups on various categorical prognostic factors while the Wilcoxon rank sum test was used to compare the treatment groups for an age difference on FEV\textsubscript{1}/FVC and D\textsubscript{co}. The following factors were entered into a multivariate model to predict percent change in FEV\textsubscript{1}/FVC and D\textsubscript{co} from before to after high-dose chemotherapy: treatment regimen, history of smoking, age, time to first post-BMT pulmonary function tests, history of lung metastases, previous chest radiotherapy, and status of pulmonary symptoms at time of last follow-up.

RESULTS

Seventy patients receiving high-dose chemotherapy containing BCNU were identified of whom 59 patients were evaluable. Of 44 consecutive patients receiving CBV, 10 patients did not have a posttreatment pulmonary function test. Of 26 consecutive patients receiving CCB, 1 patient did not have a posttreatment pulmonary function test. Therefore, a total of 59 patients were evaluable.

The patient characteristics are listed in Table 1. The CBV group was comparable to the CCB group with respect to age and pretreatment characteristics.

No pretreatment variable was significantly related to a change in D\textsubscript{co} or FEV\textsubscript{1}/FVC. No patient in the CCB group received bleomycin, but 76% of patients in the CBV group were treated with bleomycin at some point before BMT. Although a history of smoking was associated with a nonsignificant decrease in FEV\textsubscript{1}/FVC post-BMT (p=0.052), the decrease was significant (p=0.034) in smokers without a history of lung metastases in subgroup analysis.

The first pulmonary function test after high-dose chemotherapy was measured at a median of 19 days (range=8 days to 68 days) after the BCNU infusion (median, 22 days after CBV and 17 days after CCB).

Prechemotherapy and postchemotherapy pulmonary function tests demonstrated no significant change in FEV\textsubscript{1}/FVC ratio (p=0.966) but D\textsubscript{co} did decrease significantly (Table 2). The mean percent change in D\textsubscript{co} from before to after high-dose chemotherapy in all patients was a decrease of 12.1% that was significantly different from zero (p<0.001). There were significant decreases in the mean percent change in D\textsubscript{co} in both the CBV (mean decrease, 10.8%; p<0.001) and CCB group (mean decrease, 13.9%; p<0.001). There was, however, no statistically significant difference in the degree of decrease between measurements between patients receiving CBV and CCB (p=0.624). The decrease in D\textsubscript{co}/VA after treatment with CCB was not statistically significant in contrast to the decrease after treatment with CBV (Table 2).

Of the 59 evaluable patients, 30 received prednisone for decreased D\textsubscript{co} after high-dose chemotherapy in an effort to prevent or attenuate clinically evident pulmonary toxic reactions (Table 3). Twelve of the 30 patients (35%) had received CBV and 18 (72%) had received CCB. Of the 12 patients receiving CBV and receiving prednisone, 6 (50%) had symptoms or signs of pulmonary toxic reactions at the time prednisone therapy was started. Five were asymptomatic and one received prednisone for another indication (rash). Eight (32%) patients receiving CCB had symptoms or signs of pulmonary toxic reactions.

Table 2—Mean Baseline and Post-BMT Pulmonary Function Test Values After Treatment With Either CBV or CCB

<table>
<thead>
<tr>
<th></th>
<th>CBV group</th>
<th>Post-BMT</th>
<th>Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1}/FVC</td>
<td>97.8</td>
<td>98.2</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>D\textsubscript{co}</td>
<td>85.7</td>
<td>74.9</td>
<td>-10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D\textsubscript{co}/VA</td>
<td>4.21</td>
<td>3.85</td>
<td>-0.36</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CCB group</th>
<th>Post-BMT</th>
<th>Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1}/FVC</td>
<td>96.5</td>
<td>96.1</td>
<td>-0.5</td>
<td>NS</td>
</tr>
<tr>
<td>D\textsubscript{co}</td>
<td>88.8</td>
<td>74.92</td>
<td>-13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D\textsubscript{co}/VA</td>
<td>4.64</td>
<td>4.21</td>
<td>-0.44</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*D\textsubscript{co}=percent predicted corrected for hemoglobin; NS=not significant.

Table 3—Outcome of Patients Treated With Empiric Prednisone Compared With a Control Group Not Treated Empirically

<table>
<thead>
<tr>
<th></th>
<th>Empiric Prednisone</th>
<th>No Empiric Prednisone</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Subsequent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary toxic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactions, No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB, No. (%)</td>
<td>2/18 (11)</td>
<td>3/7 (43)</td>
<td>0.12</td>
</tr>
<tr>
<td>CBV, No. (%)</td>
<td>2/12 (17)</td>
<td>3/22 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Toxic reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requiring hospital admission, No. (%)</td>
<td>0</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Of the 30 patients who received prednisone, 23 (77%) never developed further pulmonary compromise (Table 3). Three developed pulmonary recurrence of cancer and 4 (13%) developed chronic pulmonary dysfunction (2 in the CCB group and 2 in the CBV group). Of the 29 patients not receiving prednisone, 6 (21%) developed pulmonary toxic reactions; 3 of 7 (43%) in the CCB group and 3 of 22 (14%) in the CBV group. One patient from each group developed severe, life-threatening pulmonary compromise requiring mechanical ventilation. No patients in the entire cohort of 59 patients have died of pulmonary toxic reactions.

**DISCUSSION**

Recent reports documenting the incidence of pulmonary toxic reactions following high-dose chemotherapy with BCNU suggest that glucocorticoids can improve symptoms and outcome once toxic reactions become manifest.8-10 In these reports, glucocorticoids were administered when pulmonary toxic reactions were clinically obvious. We have demonstrated objective evidence that empiric prednisone therapy corrects treatment-induced declines in Dco and lowers the incidence of clinically significant pulmonary toxic reactions when administered for symptomatically mild declines in Dco.

Early reports of BCNU-induced pulmonary toxic reactions suggested no benefit from glucocorticoid therapy.2 Phillips et al5 reported improvement in 50% of patients with BCNU pulmonary toxic reactions treated with glucocorticoids, perhaps reflecting earlier institution of therapy with increased awareness of the syndrome. The beneficial effects of glucocorticoids have been confirmed by others.8-10 Despite the prompt administration of glucocorticoids, however, mortality resulting from pulmonary toxic reactions still occurs in a small percentage of patients.9 In those patients treated with glucocorticoids when toxic reactions are diagnosed, most require prolonged therapy but ultimately recover. None of our patients treated empirically with prednisone have died as a result of pulmonary toxic reactions and only six have required treatment beyond 6 months after high-dose chemotherapy. This suggests that early institution of glucocorticoid therapy for mild or subclinical pulmonary dysfunction might reduce morbidity and improve survival.

The mean FEV1/FVC did not change after treatment with high-dose chemotherapy in our patients. Additionally, there was no change in mean FEV1/FVC after treatment with prednisone. It is, therefore, unlikely that the benefit of glucocorticoids in our series is due to reversal of bronchospasm or airway obstruction.

Although the mean Dco/VA decreased following high-dose chemotherapy, a statistically significant decrease could not be detected in the CCB group probably due to inadequate numbers of patients.
tested. Alveolar volume is unlikely to increase after high-dose chemotherapy; therefore, it must have remained relatively unchanged. Interestingly, the decline in mean DCO/VA was not corrected by prednisone treatment in either group. This suggests that, since the mean DCO increased, VA must also have increased in proportion to DCO after treatment with prednisone.

We could not identify patients at higher risk of having pulmonary toxic reactions after treatment with high-dose chemotherapy, although smokers tended to have a worsening of airways disease. Other investigators have similarly failed to find factors predictive of BCNU lung injury. This contrasts with previous reports suggesting identifiable risk factors for toxic reactions in patients receiving standard doses of BCNU. A recent report from Anscher et al suggests plasma levels of transforming growth factor-beta predicts subsequent development of pulmonary toxic reactions following high-dose chemotherapy. This test was not performed in our patients, but if validated, this intriguing finding suggests a potential role for prophylactic glucocorticoid therapy in patients with high plasma levels of transforming growth factor-beta.

The low incidence of pulmonary toxic reactions in our study may be due to factors other than empiric prednisone therapy. About half of our patients had pulmonary symptoms when prednisone treatment was begun. It is possible that these patients were in the early stages of drug-induced pulmonary injury and we were actually instituting early therapeutic prednisone rather than prophylactic treatment in these patients. This would be consistent with the findings of others that glucocorticoids can reverse BCNU-induced lung damage when instituted early.

Although the pulmonary toxicity of the CCB regimen for the treatment of breast cancer occurs in about 40% of patients, the incidence after CBV for the treatment of lymphoma is only about 2%. The reason for this discrepancy is uncertain but may have to do with plasma concentrations of drug. We reconstituted BCNU in two different concentrations of alcohol in our two groups of patients. Significant losses of drug, up to 25%, have been reported when BCNU is reconstituted in less than 3 mL of alcohol per 100 mg of BCNU (F.A. Bambarola, BS, personal communication on behalf of Bristol-Myers, 1993). Despite the potential for lower plasma drug levels using less alcohol in our patients receiving CBV, there was no significant difference in the decrease in DCO between the two groups after high-dose BCNU therapy. This could mean that declines in DCO are not predictive of subsequent pulmonary toxic reactions, which we doubt, or something other than BCNU-induced lung injury, such as a drug interaction with cisplatin, is contributing to the higher incidence of toxic reactions after CB. The role of drug levels cannot be disproven by our analysis, and future studies of BCNU-induced pulmonary toxic reactions should include determinations of drug levels.

Six patients in our series were refractory to glucocorticoid therapy. Two of these patients were subsequently noted to have progressive pulmonary metastases. This suggests that in patients manifesting evidence of pulmonary toxic reactions after high-dose chemotherapy, failure to respond to glucocorticoid therapy may indicate progression of pulmonary metastases.

Our study was retrospective and therefore susceptible to bias. There were no standard criteria for the initiation of prednisone therapy in our study; thus, patient selection may have biased our results. The DCO is a sensitive test for the detection of BCNU-induced pulmonary toxic reactions, but it is not very specific. Other conditions such as congestive heart failure and infection can also result in low DCO. Although we did not specifically exclude other causes of decreased DCO, we think drug-induced pulmonary toxic reaction is the most likely cause since the decreased DCO corrected with prednisone therapy alone and there was no clinical evidence of other causes present when prednisone therapy was instituted.

In conclusion, the use of BCNU in high-dose chemotherapy preparative regimens can be associated with severe pulmonary toxic reactions that usually manifest as decreased DCO in addition to other findings. One cannot predict the patients who will manifest pulmonary toxic reactions by pretreatment clinical parameters. In patients who manifest symptoms or signs of pulmonary toxic reactions or who have asymptomatic decreases in DCO, empiric treatment with prednisone will increase DCO and improve symptoms. Empiric prednisone therapy may also decrease the incidence of severe pulmonary dysfunction and may decrease mortality. Earlier institution of glucocorticoid therapy for evidence of pulmonary dysfunction is recommended.

REFERENCES
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chloroethyl)-1-nitrosurea (BCNU), NSC 4366650 and cryopreserved autologous marrow transplantation for refractory cancer. Cancer 1983; 52:1792-1802