Pulmonary Complications of Combination Therapy with Cyclophosphamide and Prednisone*

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Oral cyclophosphamide and prednisone are standard treatment for some neoplasms and necrotizing systemic vasculitis and are advocated with increasing frequency for idiopathic interstitial lung disease. During a 15-month period, we observed four cases of acute respiratory failure from Pneumocystis carinii pneumonia (PCP) in patients treated with oral cyclophosphamide and prednisone. One patient each had polyarteritis nodosa, Wegener's granulomatosis, bronchiolitis obliterans with organizing pneumonia, and chronic lymphocytic leukemia with red blood cell aplasia. Hypoalbuminemia (serum albumin level <3.0 g/dl) and daily therapy were associated with increased risk for development of PCP (p<0.05). None of the patients had leukopenia (<3,500/µl mm or neutropenia (<1,000/cumm) at diagnosis. All were negative for the human immunodeficiency virus. Patients receiving oral cyclophosphamide and prednisone may be at higher or increasing risk for PCP. A high index of suspicion and aggressive evaluation for opportunistic infection are needed in these patients; consideration for trimethoprim-sulfamethoxazole prophylaxis and development of more quantitative measures of immunosuppression are needed. (Chest 1991; 99:143-46)

IPF = idiopathic pulmonary fibrosis; CLL = chronic lymphocytic leukemia; CMl = cell-mediated immunity

Until recently, patients afflicted with certain malignant neoplasms and aggressive nonneoplastic conditions (eg, necrotizing systemic vasculitis, interstitial lung disease) had a poor prognosis and few therapeutic options. For example, patients with Wegener's granulomatosis had a mean survival of five months, and those with idiopathic pulmonary fibrosis (IPF) had a three- to four-year survival. Fauci and colleagues14 presented a series of articles documenting improved survival with polyarteritis nodosa, lymphomatoid granulomatosis, and Wegener's granulomatosis using combination therapy with cyclophosphamide and prednisone. Gadek and Allen6 extrapolated from the experience of Turner-Warwick and Haslam7 to recommend combination therapy for some patients with IPF. Investigators reported few instances of serious or life-threatening toxicity, with primary concerns about hemorrhagic cystitis or development of second malignancies,1 although recent reports document fatal infections and a variety of neoplasms associated with cytotoxic therapy.6,7 During a 15-month period, we have observed four episodes of acute respiratory failure in patients receiving daily cyclophosphamide and prednisone. During the same period, nine patients received similar therapy without major complications.

CASE REPORTS

CASE 1

A 56-year-old woman presented with confusion, sinus congestion, and multiple cavitary pulmonary infiltrates. A nasal biopsy specimen demonstrated necrotizing granulomatous inflammation, consistent with Wegener's granulomatosis. She was placed on a regimen of prednisone and cyclophosphamide (150 mg) and had a dramatic clinical response with resolution of her confusion and diminution of her infiltrates. Her rheumatologist was unable to taper her prednisone dose below 20 mg at two months, and dyspnea, hypoxemia, and diffuse pulmonary infiltrates developed. An open lung biopsy specimen showed changes consistent with drug-induced lung disease and Pneumocystis carinii cysts, without a characteristic alveolar exudate. Despite ventilatory support and appropriate management, her infiltrates progressed and the patient died. No postmortem examination was done.

CASE 2

A 71-year-old man with a malignant thymoma diagnosed in 1981 was treated with radiation therapy. A malignant left pleural effusion developed in 1986 that remained stable with prednisone therapy. His dyspnea progressed in conjunction with the development of diffuse interstitial lung disease. An open lung biopsy specimen in June 1988 demonstrated bronchiolitis obliterans with organizing pneumonia. This failed to respond to 60 mg of prednisone a day after three months, and he was then placed on a regimen of cyclophosphamide (125 mg/day) with 30 mg of prednisone. Two months later, fever and diffuse infiltrates developed and he required mechanical ventilation. A transbronchial lung biopsy specimen demonstrated P carinii. Despite improvement with trimethoprim-

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sulfamethoxazole, he remained ventilator dependent for five months and subsequently died. No postmortem examination was performed.

**Case 3**

A 60-year-old man presented with chronic cough, fever of unknown origin, and azotemia. A renal biopsy specimen showed necrotizing glomerulitis and (for presumptive polyarteritis nodosa) the patient was placed on a regimen of cyclophosphamide (150 mg) and prednisone (80 mg), which was tapered to 40 mg daily, limited by increasing azotemia. Within three months, diffuse pulmonary infiltrates, fever, and hypoxemia requiring mechanical ventilation developed. Bronchoalveolar lavage showed *P. carinii* pneumonia (PCP). Renal failure and progressive lung disease developed in the patient despite trimethoprim-sulfamethoxazole and pentamidine therapy, and he died. No postmortem examination was obtained.

**Case 4**

A 61-year-old man with a six-year history of chronic lymphocytic leukemia (CLL) with splenomegaly and red blood cell aplasia received cyclophosphamide (100 mg) and prednisone (40 mg) for six weeks. Fever, diffuse pulmonary infiltrates, and severe hypoxemia developed. A bronchoalveolar lavage demonstrated *P. carinii*, and treatment with cyclophosphamide was discontinued. On the third hospital day, despite trimethoprim-sulfamethoxazole therapy, respiratory failure developed requiring mechanical ventilation. He ultimately recovered.

**Data Analysis**

A computerized search for all patients receiving oral cyclophosphamide and prednisone during a 15-month period was performed at the National Naval Medical Center pharmacy to establish patient use of cyclophosphamide and prednisone. We restricted our analysis of cyclophosphamide and prednisone pulmonary toxicity to those patients using outpatient (oral) therapy with these agents. We also reviewed the number of patients treated with prednisone without cyclophosphamide who had CLL, bronchiolitis obliterans, or systemic vasculitis during a similar time period. Statistical comparisons were generated using Student's *t* test for parametric statistics and Fisher's exact test for nonparametric statistics. This information is presented in Table 1.

**RESULTS**

Four of 13 patients had pulmonary complications

**Table 1—Characteristics of Patients Receiving Cyclophosphamide and Prednisone and Relationship to Developing Respiratory Failure**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Respiratory Failure</th>
<th>Uncomplicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Underlying malignancy</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>65.5</td>
<td>51</td>
</tr>
<tr>
<td>Duration of therapy, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Range</td>
<td>6-12</td>
<td>12-52</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.0†</td>
<td>3.8</td>
</tr>
<tr>
<td>Range</td>
<td>2.2-4.5</td>
<td>3.1-4.4</td>
</tr>
<tr>
<td>Daily C/P</td>
<td>4†</td>
<td>1</td>
</tr>
<tr>
<td>PMN &lt;1,000/cu mm</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lymphs &lt;500/cu mm</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*C = cyclophosphamide; P = prednisone; PMN = polymorphonuclear leukocytes; lymphs = lymphocytes.

†p < 0.05.

**Discussion**

Progressive and ultimately fatal conditions such as cancer, necrotizing systemic vasculitis, and IPF justify some of the potential risk associated with immunosuppressive therapy. Cyclophosphamide reduces the circulating pool of mononuclear phagocytes producing both monocytopenia and lymphopenia. Although a total peripheral lymphocyte count of less than 500/cu mm is associated with significant immunosuppression, infection risks are more closely associated with total granulocyte counts. *Pneumocystis carinii* pneumonia has emerged as a frequent opportunistic pathogen in develop, including PCP. Three of the nine patients without complications had myeloma, three had non-Hodgkin's lymphoma, and one each had breast cancer, Wegener's granulomatosis, and systemic lupus erythematosus. Patients in whom PCP developed had lower serum albumin levels and received daily doses of cyclophosphamide and prednisone. Three of the four patients in whom PCP developed had serum albumin levels less than 3.0 g/dl (30 g/L), while none of the intermittent cyclophosphamide and prednisone group had albumin levels less than 3.0 g/dl (30 g/L) during the survey period (p = 0.018). Three of four patients with acute toxicity had less than 500 lymphocytes per cubic millimeter (by differential cell count), while the fourth had CLL. Relative proportions of lymphocytes were not determined. None of the patients who had development of respiratory failure had a total WBC count of less than 3,000/cu mm or total polymorphonuclear leukocytes of less than 1,500/cu mm. There was no significant difference in the mean age of the two groups. Among patients who had complications develop, cyclophosphamide doses ranged from 100 to 150 mg daily, with prednisone 20 to 40 mg daily at the time of complications. In the group without complications, cyclophosphamide was never used for more than five days per month, at a dose of 800 mg/day. Only two of the latter group were receiving "immunosuppressive" therapy, while seven received cancer chemotherapy with immunosuppression as a secondary effect. Sustained neutropenia was seen in neither group. During the specified time period, all patients who had PCP develop in our institution had either the acquired immunodeficiency syndrome (AIDS) or were receiving oral cyclophosphamide and prednisone. Four of six patients with CLL, systemic vasculitis, or bronchiolitis obliterans receiving oral cyclophosphamide and prednisone during this period had PCP develop, while none of 32 patients with the same conditions (CLL, 22 patients; bronchiolitis obliterans, five patients; vasculitis, five patients) receiving prednisone without cyclophosphamide had PCP develop (p = .0002). No patient with PCP in our institution between 1986 and 1990 has received prednisone alone.
immunosuppressed patients, particularly those with AIDS.\textsuperscript{10} Both cyclophosphamide and prednisone have been implicated as capable of producing immunosuppression contributing to the development of PCP, presumably related to T-cell dysfunction.\textsuperscript{11} O'Donnell and associates\textsuperscript{12} have shown greater suppression of neutrophil alveolitis in IPPF with either cyclophosphamide or cyclophosphamide and prednisone than with prednisone alone. The quantitative effects of cyclophosphamide and prednisone on pulmonary cell-mediated immunity are less clear, although Hughes et al\textsuperscript{13} established that the likelihood of PCP relates to the intensity of immunosuppression.

The contribution of cyclophosphamide and prednisone to impaired cell-mediated immunity is not new information,\textsuperscript{14} although the frequency of complications varies. \textit{Pneumocystis carinii} has previously been identified as a cause of respiratory morbidity in patients with lymphoma receiving combination chemotherapy.\textsuperscript{15} Thirty of 39 patients without AIDS who had PCP develop were receiving both prednisone and cytotoxic therapy.\textsuperscript{16} Three patients died of PCP among 44 fatalities with systemic lupus erythematosus in one series.\textsuperscript{17} Twelve of 53 patients with PCP whose cases were reported by the Mayo Clinic were receiving steroids alone, while four were receiving cytotoxic therapy without steroids.\textsuperscript{18} However, among 71 patients with polyarteritis nodosa and Churg-Strauss angiitis receiving cytotoxic therapy (including cyclophosphamide and prednisone in 45 patients), no cases of PCP are presented.\textsuperscript{19} Individual cases of PCP may not be deemed "newsworthy" by physicians using immunosuppression, leading to possible case under-reporting. Our experience suggests that PCP is the principal early risk associated with daily oral cyclophosphamide and prednisone therapy. Cyclophosphamide pulmonary toxicity is an uncommon entity, a diagnosis of exclusion, and represents an idiosyncratic pulmonary reaction characterized by hyperplasia of type 2 pneumocytes.\textsuperscript{20} Limited use of open lung biopsy and lack of reporting requirements of drug-induced lung disease may result in underdiagnosis and under-reporting of pulmonary drug toxicity.\textsuperscript{21} Only one of our four patients developing acute respiratory failure had pulmonary drug toxicity from cyclophosphamide substantiated by open lung biopsy specimen.

The frequency with which pulmonary complications developed in our patients in conjunction with daily cyclophosphamide and prednisone therapy is unique. All patients had respiratory failure develop that required mechanical ventilation, and three eventually died. Two of the patients had underlying neoplasms, although neither CLL nor malignant thymoma are ordinarily associated with PCP. Our patients with CLL, vasculitis, and bronchiolitis obliterans treated with daily prednisone with or without intermittent alkylating agents have not had PCP develop. We believe this strongly implicates the daily administration of cyclophosphamide in the pathogenesis of PCP. Although defective antigen presentation in CLL may account for some defects in cell-mediated immunity (CMI), some defects in CMI are attributed to therapy.\textsuperscript{22} The reduced serum albumin level seen in these patients, reflecting diminished visceral protein stores, may have contributed to immunosuppression and development of PCP.\textsuperscript{23}

The treatment protocol of Fauci et al\textsuperscript{4} for Wegener's granulomatosis included initiation of cyclophosphamide therapy at an oral dose of 2 mg/kg of body weight, continued for variable periods. Simultaneously, prednisone (1 mg/kg of body weight) was administered for two to four weeks until cyclophosphamide effects were noted. The prednisone dosage was then tapered over one to two months to an alternate-day regimen.\textsuperscript{1} Leavitt and Fauci\textsuperscript{24} have more recently noted that by the third month of therapy, "the patient should be maintained on 1 mg/kg of prednisone on alternate days." The duration (but not the doses) of daily cyclophosphamide and prednisone in the patients in whom we diagnosed PCP modestly exceeded Fauci's guidelines, because limited clinical responses to therapy prevented further prednisone tapering. None of the patients had development of PCP coincident with withdrawal of prednisone therapy. It is unknown whether strict adherence to the Fauci protocol would have prevented development of PCP. Only one of the patients (Case 1) had been recently hospitalized, making in-hospital acquisition of the agent unlikely. The patients had four different diagnoses and had received care from four different physicians, rendering systematic prescription or follow-up errors unlikely.

The finding of severe lymhopenia in three of the four patients is a tantalizing explanation to account for the toxicity seen, and none of the four patients had either profound granulocytopenia or leukopenia. Sere lymhopenia (T4 cells <200/cu mm) has been associated with increasing frequency of PCP in several studies in patients with AIDS.\textsuperscript{24,25}

Although we cannot fully explain the frequency of PCP with daily cyclophosphamide and prednisone therapy in our institution, we believe our experience provides convincing evidence that the combination of daily doses of cyclophosphamide and prednisone contributed to development of PCP. We believe the frequency and severity of complications suggests the following recommendations: (1) strong consideration of PCP in any patient receiving daily doses of cyclophosphamide and prednisone who has development of symptoms or signs of pulmonary infection; (2) consideration of prophylactic trimethoprim-sulfamethoxazole therapy in these patients; and (3) possibly limiting use of daily doses of cyclophosphamide/
prednisone in IPF to patients with histologically proven disease who have not responded to initial prednisone therapy, until further prospective data substantiate a favorable change in the natural history of IPF with initial cytotoxic therapy. Serial monitoring of carbon monoxide diffusing capacity (Dco), which is generally reduced when PCP is diagnosed, could potentially detect subclinical pulmonary function changes. Because the duration of symptoms with PCP associated with immunosuppressive diseases other than AIDS is short, and previous frequency of PCP with cyclophosphamide and prednisone is low, the value of serial Dco determination is uncertain. Evaluation of quantitative measurements of cell-mediated immunity (eg, peripheral helper T cells, bronchoalveolar lavage, delayed hypersensitivity testing) and their correlation with "safe" and effective immunosuppression may establish better guidelines for "appropriate" immunosuppression. Although cyclophosphamide is sometimes considered a means to reduce steroid side effects, it carries a significantly different set of risks, both acute (hemorrhagic cystitis and opportunistic infection) and chronic toxicity (bladder carcinoma and hematologic malignancy), which may be either underreported or increasing in incidence.

References