Pulse Intravenous Cyclophosphamide Therapy in Pemphigus

Mary E. Fleischli, MD; Rachel H. Valek, BS; Amit G. Pandya, MD

Background: Adjuvant therapy is commonly used in pemphigus to mitigate the high morbidity and mortality associated with the use of corticosteroids and improve disease control. However, these adjuvant agents are not without adverse effects of their own, including an increased risk of malignancy with the use of oral immunosuppressives. Intravenous pulse cyclophosphamide, which may be more efficacious and less toxic than oral immunosuppressives, has been used successfully in the treatment of pemphigus.

Objective: To review 9 patients with severe or previously recalcitrant pemphigus who were treated with intravenous pulse cyclophosphamide therapy.

Results: Six of the 9 patients responded to therapy, with 2 patients achieving remission from skin lesions. Five patients were able to decrease their daily dose of prednisone, and 1 was able to discontinue the use of prednisone completely. Most patients experienced minimal or no adverse effects.

Conclusions: Intravenous pulse cyclophosphamide may be an alternative treatment option in patients with pemphigus recalcitrant to standard therapy. The decreased cumulative dose of cyclophosphamide observed with monthly pulse doses may reduce the incidence of secondary malignancies when compared with continuous oral therapy. Controlled trials are needed to further evaluate the efficacy of this mode of therapy.

Arch Dermatol. 1999;135:57-61

EMPHIGUS IS an autoimmune-blistering disease of the skin and mucous membranes mediated by autoantibodies against surface antigens of keratinocytes. The predominant therapy for this disorder continues to be corticosteroids. Prior to the development of corticosteroid therapy in the 1950s, the mortality rate for patients with pemphigus was greater than 90%. Since that time, mortality has declined, and is now estimated to be 5% to 15%. However, the large doses of steroids and prolonged therapy needed to suppress the disease often results in serious adverse effects. These adverse effects, rather than the disease itself, account for a significant proportion of the morbidity and mortality associated with pemphigus today.

To decrease the exposure to corticosteroids, the use of steroid-sparing agents in pemphigus has become common. These agents include azathioprine, cyclosporine, gold, dapsone, antimalarials, and cyclophosphamide. However, these treatment modalities may cause adverse reactions of their own. For example, daily oral cyclophosphamide can lead to hemorrhagic cystitis, and is associated with an increased risk of malignancy after prolonged use. Intravenous (IV) pulse cyclophosphamide, with or without corticosteroids, has also been used for the treatment of pemphigus. This method of administration may decrease adverse effects and risk of malignancy associated with daily use of oral cyclophosphamide, while maintaining or improving efficacy.

In this retrospective study, we reviewed the records of 9 patients with pemphigus who were treated with IV pulse cyclophosphamide. Patients treated with this modality had disease that was either severe and life-threatening or recalcitrant to multiple therapies.

RESULTS

The response to therapy with IV pulse cyclophosphamide is summarized in Table 2. Of 9 patients previously refractory to therapy, 6 had an excellent or good response, 2 had minimal or no response, and 1 (patient 5) died. The patient who died only received 3 pulses and died 1 month...
PATIENTS AND METHODS

The medical records of 9 patients treated with pulse intravenous cyclophosphamide were reviewed. Two of these patients have been described previously.7,16 Herein we present long-term follow-up of these 2 patients. All patients had a diagnosis of pemphigus based on skin biopsy findings, including direct or indirect immunofluorescence. Patient demographic data are presented in Table 1. Of the 9 patients, 8 had cutaneous lesions and 5 had mucosal lesions. All patients had been previously treated with prednisone. Adjuvant therapies used in the past included 7 patients treated with intramuscular gold, 8 with azathioprine, 4 with dapsone, and 1 with topical cyclosporine for oral mucosal disease. Adjuvant therapies had been discontinued because of lack of efficacy or adverse reactions.

The standard protocol for pulse cyclophosphamide therapy required the presence of severe disease or failure to respond to less toxic therapies. All patients had a complete blood cell count, serum chemistry screen, urinalysis, and, if female, a pregnancy test before beginning treatment. Monthly IV cyclophosphamide was initiated as described by Pandya and Sontheimer17 at a dose of 0.5 to 1.0 g/m² of body surface area. The medication was added to 250 mL of isotonic sodium chloride solution and infused over 1 hour. Patients were instructed to drink a 0.36-L (12-oz) glass of water every 2 hours while awake for 3 days, beginning 24 hours before the cyclophosphamide infusion. A follow-up complete blood cell count was obtained 10 to 14 days afterward, and if the white blood cell count was greater than 20 × 10⁹/L, monthly pulse cyclophosphamide was continued. In recent years, 10 mg of IV ondansetron has been substituted for previously used prechemotherapy medications such as diphenhydramine because of its superior efficacy in preventing nausea and vomiting. The dose of IV cyclophosphamide was increased by 100 to 250 mg per dose if the white blood cell count did not decrease by more than 20 × 10⁹/L at the 2-week nadir. Liver function tests and a urinalysis were performed monthly to screen for liver toxic effects and hemorrhagic cystitis. All patients were treated with a concurrent low dose of oral cyclophosphamide (50 mg/d) and prednisone except for patient 2, who was treated with pulse cyclophosphamide alone because of nausea from the use of oral cyclophosphamide. The prednisone dose was adjusted according to disease severity. Patient 1 was also initially treated with 2 successive daily plasmapheresis sessions for rapid resolution of severe disease. The initial dose of IV cyclophosphamide ranged from 500 to 1000 mg. The highest dose administered ranged from 750 to 2000 mg, while the number of pulses ranged from 3 to 24 (Table 2). Once control of disease had been achieved, oral cyclophosphamide was discontinued, followed by discontinuation of IV pulse cyclophosphamide several months later. Control of disease was achieved within 2 to 5 months in all patients who responded to the therapy.

After an excellent response to therapy, patient 1 has continued to receive monthly pulse doses of 1000-mg IV cyclophosphamide with good disease control. Patient 3 had complete resolution of disease after 11 cycles but flared 8 months later. This flare resolved after 3 additional monthly doses of cyclophosphamide after which his disease was controlled with low-dose prednisone (10 mg/d) and topical corticosteroids. Patient 4 had a good response to therapy but died shortly after her last dose of a myocardial infarction. Her disease was under good control at the time of death. Patient 6 was able to discontinue prednisone and was free of disease after 7 cycles. Afterward, the patient had 2 disease flares that were not as severe as previous flares and that were controlled with 2- to 3-month short courses of prednisone and topical steroids. Patient 9 had an excellent response to therapy after 8 pulse doses of IV cyclophosphamide and remained clear of disease for 1 year; however, the patient’s disease recently began to flare, prompting a resumption of pulse cyclophosphamide therapy.

COMMENT

Cyclophosphamide is an alkylating agent that disrupts cell growth and mitotic activity by cross-linking DNA,15 and, after her last dose, secondary to cardiac failure. Five patients (patients 1, 3, 4, 7, and 9) were able to decrease their daily dose of prednisone substantially, and patient 6 was able to discontinue prednisone completely. Most patients experienced minimal or no adverse effects, including 4 who developed nausea, 2 with leukopenia, and 1 with sepsis who was successfully treated with intravenous antibiotics. Figure 1 and Figure 2 demonstrate improvement in a patient with pemphigus vulgaris from our series.

Table 2. Response to Therapy*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Dosage, mg</th>
<th>Highest Dosage, mg</th>
<th>No. of Pulses</th>
<th>Concomitant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>750</td>
<td>1100</td>
<td>24</td>
<td>Plasmapheresis (&gt;2), prednisone, and oral cyclophosphamide</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>1500</td>
<td>20</td>
<td>Oral cyclophosphamide</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>1000</td>
<td>14</td>
<td>Oral cyclophosphamide and prednisone</td>
</tr>
<tr>
<td>4</td>
<td>500</td>
<td>800</td>
<td>6</td>
<td>Oral cyclophosphamide and prednisone</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>750</td>
<td>3</td>
<td>Oral cyclophosphamide and prednisone</td>
</tr>
<tr>
<td>6</td>
<td>500</td>
<td>750</td>
<td>7</td>
<td>Oral cyclophosphamide and prednisone</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
<td>850</td>
<td>7</td>
<td>Oral cyclophosphamide and prednisone</td>
</tr>
<tr>
<td>8</td>
<td>500</td>
<td>800</td>
<td>12</td>
<td>Prednisone</td>
</tr>
<tr>
<td>9</td>
<td>1000</td>
<td>2000</td>
<td>8</td>
<td>Prednisone and azathioprine</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable.
†Excellent indicates severe or moderate disease improving to absence of disease, none; good, severe disease improving to moderate or mild disease; minimal, moderate disease improving to mild disease; and none, no change or worsening of disease.
like azathioprine, has been used as a steroid-sparing agent in the treatment of pemphigus. However, daily oral cyclophosphamide can lead to a variety of adverse effects including myelosuppression, nausea, alopecia, hemorrhagic cystitis, ovarian failure, and teratogenicity.\textsuperscript{15,16,20} Daily oral cyclophosphamide is also associated with an increased incidence of malignancies,\textsuperscript{15,16,21} including a 31- to 33-fold increase in bladder carcinoma\textsuperscript{22,23} and an 11-fold increase in lymphomas\textsuperscript{23} after prolonged use. In contrast, monthly high-dose IV cyclophosphamide causes minimal adverse effects, with no reports of bladder cancer in patients treated with this form of therapy.\textsuperscript{20} The fact that the cumulative dose of cyclophosphamide with monthly pulse doses is lower than continuous oral therapy may account for the lower incidence of secondary malignancies. Adequate hydration is important when treating with cyclophosphamide to prevent hemorrhagic cystitis. Patients receiving oral cyclophosphamide are instructed to take the entire daily dose of medication in the morning and drink four 0.36-L (12-oz) glasses of water before noon each day.

Although intravenous pulse cyclophosphamide is associated with fewer adverse reactions than oral therapy, teratogenicity\textsuperscript{24} and sustained amenorrhea\textsuperscript{25} have been reported. However, the incidence of amenorrhea is lower than that associated with daily oral therapy.\textsuperscript{26} Additionally, a study of 55 patients treated with weekly low-dose pulses of IV cyclophosphamide reported menstrual irregularities in patients receiving concomitant oral cyclophosphamide but not in patients treated with pulse cyclophosphamide alone.\textsuperscript{27}

Intravenous pulse cyclophosphamide has been used in the treatment of several diseases, including neuropsychiatric lupus erythematosus,\textsuperscript{28} lupus nephritis,\textsuperscript{29} Wegener

### Table 1. Patient Demographic Information Before Treatment With Pulse Cyclophosphamide

<table>
<thead>
<tr>
<th>Patient/Age, y/Sex</th>
<th>Type of Pemphigus</th>
<th>Severity of Disease</th>
<th>Prior Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/58/M</td>
<td>Vulgaris</td>
<td>Severe cutaneous, moderate mucosal</td>
<td>Prednisone, azathioprine, gold</td>
</tr>
<tr>
<td>2/53/F</td>
<td>Vulgaris</td>
<td>Severe mucosal</td>
<td>Prednisone, dexamethasone (Decadron), topical cyclosporine, azathioprine, gold, dapsone</td>
</tr>
<tr>
<td>3/33/M</td>
<td>Vulgaris</td>
<td>Moderate cutaneous, moderate mucosal</td>
<td>Prednisone, azathioprine, dapsone, gold</td>
</tr>
<tr>
<td>4/43/F</td>
<td>Erythematous</td>
<td>Severe cutaneous</td>
<td>Prednisone, azathioprine, adrenocorticotropic hormone injections</td>
</tr>
<tr>
<td>5/74/F</td>
<td>Vulgaris</td>
<td>Moderate cutaneous, moderate mucosal</td>
<td>Prednisone, gold, azathioprine</td>
</tr>
<tr>
<td>6/31/F</td>
<td>Vulgaris</td>
<td>Moderate cutaneous, moderate mucosal</td>
<td>Prednisone, dapsone, azathioprine, gold, oral cyclophosphamide</td>
</tr>
<tr>
<td>7/53/M</td>
<td>Vulgaris</td>
<td>Moderate cutaneous</td>
<td>Prednisone, gold, azathioprine</td>
</tr>
<tr>
<td>8/63/F</td>
<td>Follicaeous</td>
<td>Severe cutaneous</td>
<td>Prednisone</td>
</tr>
<tr>
<td>9/51/F</td>
<td>Vulgaris</td>
<td>Severe cutaneous</td>
<td>Prednisone, dapsone, azathioprine, gold, oral cyclophosphamide</td>
</tr>
</tbody>
</table>

*Cutaneous disease severity: mild, less than 20 blisters; moderate, 20 to 40 blisters; and severe, more than 40 blisters. Mucous membrane disease severity: mild, 1 to 5 small erosions; moderate, 5 to 10 erosions; and severe, more than 10 erosions or extensive erosions.
granulomatosis,\textsuperscript{30} Behçet disease,\textsuperscript{31} and pyoderma gangrenosum associated with rheumatoid arthritis.\textsuperscript{32} Low-dose oral cyclophosphamide was not given concurrently in most of these trials. The superior efficacy and fewer adverse effects of IV cyclophosphamide compared with oral cyclophosphamide or corticosteroids alone for lupus nephritis\textsuperscript{29} led to its use in other autoimmune diseases, such as pemphigus. In 1988, Pasricha et al\textsuperscript{18} reported the combination of monthly high-dose dexamethasone and IV cyclophosphamide along with low-dose oral cyclophosphamide in the treatment of 79 patients with pemphigus. Between 1982 and 1987, 25 (32\%) of the patients achieved complete remission of their disease (with discontinuation of all medication), and 25 (32\%) were controlled with oral cyclophosphamide alone (50 mg/d). They reported no serious adverse reactions. Additionally, patients experienced freedom from steroid-induced adverse effects such as obesity, osteoporosis, hypertension, diabetes, peptic ulcer disease, and cataracts. Several years later, Surrinder and Kanwar\textsuperscript{19} used the same regimen to treat 50 patients with pemphigus. At the time their report was published, 23 patients (46\%) had improvement of disease and were still receiving pulse therapy while 5 patients (10\%) had achieved control of their disease with pulse therapy and were now receiving oral cyclophosphamide therapy (30 mg/d) alone. A preliminary report of 2 patients treated in our center with pulse cyclophosphamide, oral cyclophosphamide, and prednisone demonstrated an excellent response with minimal adverse effects from treatment.\textsuperscript{37} These 2 patients (patients 3 and 6) have been followed up for more than 5 years and have only required minimal therapy with 2- to 3-month courses of oral and topical steroids for mild recurrences.

Other modalities used for the treatment of pemphigus have had variable response rates that compare favorably with that of our patients. Azathioprine has produced a remission rate of 45\% in a previous study\textsuperscript{7} and is one of the most commonly used agents for pemphigus. It has fewer adverse effects than cyclophosphamide and may be preferred over other, more toxic therapeutic modalities. Plasmapheresis coupled with an immunosuppressive agent has shown a response rate of 64\%, but is usually reserved for severe pemphigus unresponsive to conventional therapy.\textsuperscript{33} Recently, pulse doses of IV corticosteroids have produced a response rate of 67\% in patients who were unresponsive to low doses of prednisone.\textsuperscript{34}

In our study of 9 patients treated with pulse cyclophosphamide and low-dose oral cyclophosphamide, 6 had an excellent or good response, 2 had a minimal response, and 1 died before a response could be ascertained. Of 2 patients who died, neither death was believed to be related to the disease, as blistering was under control at the time of death and there were no serious complications from cyclophosphamide therapy. Because these patients were receiving high doses of corticosteroids, their deaths, which were attributable to cardiac failure and myocardial infarction, respectively, may have been contributed to by this therapy; however, one cannot rule out cyclophosphamide therapy as a contributory cause of death. Most patients had adverse effects from IV cyclophosphamide therapy. Four patients had nausea, but the use of ondansetron has decreased the incidence of this complication substantially. Two patients with excellent responses developed serious adverse effects; neutropenia and sepsis in one, and neutropenia alone in another. Indeed, pulse cyclophosphamide therapy should be considered only in patients with severe disease that is recalcitrant to standard therapy. Dermatologists who are unfamiliar with the administration of IV cyclophosphamide and its adverse effects may find it helpful to consult with their oncology colleagues, who can help in the treatment of potential patients.

Lack of controlled studies and variation in treat-
ment protocols among different centers makes this form of therapy, as with other forms of pemphigus treatment, difficult to evaluate. Further evaluation of pulse cyclophosphamide for pemphigus will require the completion of larger, controlled trials.

Accepted for publication May 18, 1998.


We thank Anthony L. Meyers, MD, for contributing a patient to this series.

Reprints: Amit G. Pandya, MD, Department of Dermatology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75233-9069 (e-mail: Apandy@mednet.swmed.edu).

REFERENCES