Objective: To determine the efficacy of multimodality biologic response therapy for patients with cutaneous T-cell lymphoma (CTCL).

Design: Retrospective cohort study over a 14-year period.

Setting: Tertiary care university hospital.

Patients: A consecutive sample of patients was studied, all 47 of whom carried the clinical and laboratory diagnosis of CTCL: 68% of patients had stage III or IV disease, and 89% had circulating malignant T cells.

Interventions: All 47 patients received photopheresis for 6 or more cycles. Thirty-one patients received treatment with a combination of photopheresis and 1 or more systemic immunostimulatory agents, including interferon alfa, interferon gamma, sargramostim, or systemic retinoids for 3 or more months.

Main Outcome Measures: Differences in pretreatment prognostic factors, response rates, and survival between patients receiving multimodality therapy and single-modality therapy or historical controls.

Results: A total of 79% of patients responded to therapy: 26% had complete remission, and 53% had a partial remission. Median survival from initiation of therapy was 74 months. Median survival for patients with stages III and IV and peripheral blood involvement was 55 months compared with 31 months for historical controls. Compared with the photopheresis monotherapy group, the patients receiving combination immunomodulatory therapy had a worse prognosis at the time of treatment initiation based on multiple prognostic factors. The positive response rates and median survival times were 84% and 74 months, respectively, compared with 75% and 66 months, respectively, for the combination immunomodulatory and photopheresis monotherapy groups (P = .47 for positive response rates and P = .51 for survival).

Conclusions: Patients with advanced CTCL and multiple poor prognostic factors who receive treatment with combination immunomodulatory therapy experience higher clinical response rates and longer survival than historical controls. Although the group who received combination therapy had worse prognostic factors at baseline, they had better response rates and overall survival compared with those receiving photopheresis monotherapy.

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CTANEOUS T-CELL lymphomas (CTCLs) are skin-invasive, T-cell, non-Hodgkin lymphomas characterized by a clonal proliferation of malignant T lymphocytes. Early-stage disease is usually confined to the skin as patches or plaques. As the disease progresses, patients can develop cutaneous tumors or erythroderma and associated peripheral blood, lymph node, and visceral organ involvement. The prognosis for patients with CTCL is dependent on stage, as determined by type and extent of skin lesions and degree of extracutaneous involvement. Cutaneous tumors, erythroderma, peripheral blood involvement, lymph node or visceral invasion, and eosinophilia denote a poor prognosis. A recent review of 106 cases of CTCL with erythroderma treated with psoralen plus UV-A irradiation (PUVA), radiation therapy, or systemic chemotherapy, alone or in combination, reported a median survival of approximately 43 months, or 3.6 years, from the first treatment date.

A variety of studies have suggested that the Sézary cell is usually derived from the T-helper type 2 subset of CD4+ lymphocytes. This is reflected in the observations that the lymphoid cells from pa-
PATIENTS AND METHODS

PHOTOPHERESIS PROCEDURE

All patients were treated with the UVAR photopheresis system (Therakos, West Chester, Pa) as previously described. The entire procedure required about 4 hours. Plasma psoralen levels were not routinely measured. However, if a patient failed to respond after 4 or 5 cycles of photopheresis, we measured plasma psoralen levels or empirically increased the psoralen dose.

TREATMENT PROTOCOL

Forty-seven patients received a minimum of 6 cycles of photopheresis between January 1985 and December 1998. All patients underwent a pretreatment assessment, which included a physical examination, skin biopsy for definitive diagnosis, routine laboratory studies, electrocardiography, and roentgenography of the chest. In addition, all patients had peripheral blood examined for the presence of atypical cells (Sezary cells). This was accomplished by light microscopic examination of 1-µm sections of the buffy coat as previously described.

Most patients also had fluorescence-activated cell sorter analysis performed on peripheral blood for the cell surface markers CD3, CD4, CD7, and CD8 and/or Southern blot analysis of the β chain gene of the T-cell receptor to determine whether an expanded clonal population of T cells was present. Furthermore, most patients who had palpable lymphadenopathy before treatment had lymph node biopsies performed. On the basis of this evaluation, patients were assigned a disease stage according to a previously defined staging system for CTCL (Table 1 and Table 2).

Present criteria for receiving photopheresis include extensive skin involvement and more than 5% circulating Sézary cells detected on buffy coat analysis. However, when photopheresis was in its early development, patients with any stage of cutaneous disease, with or without peripheral blood involvement, were eligible for treatment. Responses in some of these early patients are included in the present study and served to establish the current treatment criteria.

Continued on next page
therapy and historical controls for the treatment of advanced CTCL.

| RESULTS |

PATIENT CHARACTERISTICS

Forty-seven patients with histopathologically confirmed CTCL were treated with at least 6 cycles of photopheresis between January 1985 and December 1998. Table 3 summarizes the baseline characteristics of the patient population. Most patients had advanced disease at the time treatment was initiated: 32 (68%) of the 47 patients had stage III or IV disease; 42 (89%) of the 47 patients had peripheral blood involvement as determined by the presence of more than 5% atypical cells detected by 1-µm section analysis of peripheral blood Buffy coats.

PATIENT CHARACTERISTICS BY THERAPY

Thirty-one (66%) of the 47 patients received combination biologic response therapy whereas 16 (34%) received extracorporeal photopheresis monotherapy. Table 4 summarizes the baseline characteristics of these 2 separate treatment populations. Differences between the 2 populations were statistically significant for the mean CD4+/CD8+ ratio (P = .006). Differences in the percentage of patients with greater than 5% circulating Sézary cells (P = .07) and for elevated WBC (P = .07) at the time of treatment initiation were nearly statistically significant. Although there seemed to be a trend toward higher Sézary counts seen on Buffy coat examination in patients who received combination therapy, there was no statistically significant difference in this parameter between the 2 therapeutic populations (P = .18). There were no significant differences between the 2 treatment groups.
in mean LDH level (P = .99) or stage of disease at treatment initiation (P = .47).

**THERAPEUTIC MODALITIES**

All 47 patients received a minimum of 6 months of photopheresis therapy. Thirty-one of the 47 patients received one or more adjuvant agents in combination with photopheresis for at least 3 months. The most common adjuvant immunostimulatory agent used in combination with photopheresis was interferon alfa (n = 30) followed by systemic retinoids (n = 21) and sargramostim (n = 15) (Table 5). The types of retinoids used included etretinate, acitretin, isotretinoin, and all-trans retinoic acid. Some of the patients received focal treatment with topical nitrogen mustard or carbustine (n = 35), topical steroids (n = 43), or γ irradiation (n = 11). A small number of patients also received combination immunostimulatory treatment group.

**RESPONSE TO THERAPY**

Twelve (26%) of the 47 patients experienced a complete remission. Twenty-five (53%) of the patients had a partial remission with at least a 50% reduction of skin and peripheral blood disease. The overall positive response rate, including complete and partial responders, was 37 (79%) of 47. Eight (17%) of the patients were considered nonresponders. Only 2 patients (+%) experienced progression of disease (Table 6). The first patient had stage IVB disease with multiple cutaneous tumors, extensive lymphadenopathy; an enlarged spleen; 7% Sézary cells onuffy coat examination; normal WBC, LDH levels, and CD4+/CD8+ ratio; and a clonal T-cell gene rearrangement in the peripheral blood by polymerase chain reaction when photopheresis was started. He had been treated with topical nitrogen mustard, topical carbustine, etretinate, PUVA, γ irradiation, interferon alfa, and intralesional kenalog prior to starting photopheresis. He received 7 cycles of photopheresis, 5 of which were combined with sargramostim. The patient’s condition progressively declined during that time. All immunomodulatory therapies were discontinued, and the patient began therapy with systemic chemotherapy. He died after receiving 3 months of chemotherapy. The second patient had stage IIB disease, also with multiple cutaneous nodules, no Sézary cells on buffy coat examination, normal WBC, an LDH level of 626 U/L (normal, ≤620 U/L), and a CD4+/CD8+ ratio of 2.6 (normal, ≤2) when photopheresis was initiated. She had received γ irradiation, multidrug systemic chemotherapy, PUVA, topical nitrogen mustard, and systemic steroids prior to starting photopheresis. She received 6 cycles of photopheresis monotherapy. Her disease rapidly progressed and she was lost to follow-up soon after her last treatment.

Twenty-six (84%) of the 31 patients in the combination immunostimulatory treatment group experienced either a complete or partial clinical response. Six patients (20%) had a complete response, 20 (65%) had a partial response, 4 (13%) had no response, and 1 (3%) had progression of disease. Of the 16 patients who received photopheresis monotherapy, 12 (75%) had a positive response. In this group, 6 (38%) were complete responders, 6 (38%) were partial responders, 3 (19%) did not respond to therapy, and 1 (6%) had progressive disease (Table 7). The differences in positive response rates between the 2 therapeutic groups were not statistically significant (P = .47). None of the patients experienced greater than grade 1 toxic effects, according to the common toxicity criteria of the National Cancer Institute.
The median survival of all 47 patients calculated from the first treatment date using the Kaplan-Meier actuarial survival curve was 74 months (6.2 years) (Figure 1). Most (68%) of the patients had stage III or IV CTCL. Kaplan-Meier survival curves were also calculated to compare survival between patients with early-stage disease (stages I and II) and advanced disease (stages III and IV) (Figure 2). Patients with late-stage disease experienced a median survival of 55 months (4.6 years), whereas patients with early stage disease had a median survival of 92 months (7.7 years). The difference in survival between these 2 groups was statistically significant (P = .03).

To evaluate for a possible difference in survival between patients treated with multimodality biologic response therapy and those who received extracorporeal photopheresis monotherapy, we calculated survival curves separately for the 2 groups (Figure 3). The median survival for the patients undergoing combination therapy was 74 months (6.2 years), whereas the median survival for the monotherapy group was 66 months (5.5 years). Survival differences for the 2 treatment groups were not statistically significant (P = .51).

**COMMENT**

Extracorporeal photopheresis is an established and effective treatment for advanced CTCL. Several groups have reported positive response rates ranging from 50% to 80% for patients with advanced-stage CTCL. Photopheresis may also prolong patient survival. Gottlieb et al reported a median survival of longer than 100 months from the time of diagnosis in patients with advanced-stage disease and peripheral blood involvement treated with a minimum of 6 months of photopheresis compared with a median survival of 30 to 40 months in historical controls.

Although the precise mechanism of action of photopheresis has not been determined, exposure of leukocytes to UV-A following uptake of 8-methoxypsoralen results in cross-linking of DNA and eventual apoptotic cell death. Murine skin transplantation models indicate that the treated leukocytes are altered in some fashion such that, when reinfused, a specific anticlonotypic immune response directed toward the pathogenic cells develops. Therefore, the overall integrity of the immune response is believed to be a critical factor for patient responsiveness to photopheresis monotherapy.

Interferon alfa is a potent biologic agent that has powerful antiproliferative, immunostimulatory, and differentiation-inducing activities. Clinical trials have shown response rates of 50% to 80% in patients with CTCL receiving systemic interferon alfa. It also exerts substantial immune augmentative effects on cytotoxic T-cell function and can reverse cytokine and immune abnormalities in Sézary syndrome. Administration of sargramostim may enhance antigen presentation and lead to an augmented antitumor response to the apoptotic T cells, and systemic retinoids can induce T-helper type 1

### Table 4. Baseline Characteristics by Therapeutic Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combination Therapy</th>
<th>Photopheresis Monotherapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient total</td>
<td>31 (66)</td>
<td>16 (34)</td>
<td>. .</td>
</tr>
<tr>
<td>Stage of disease</td>
<td></td>
<td></td>
<td>.47</td>
</tr>
<tr>
<td>I and II</td>
<td>11 (35)</td>
<td>4 (25)</td>
<td>. .</td>
</tr>
<tr>
<td>III and IV</td>
<td>20 (65)</td>
<td>12 (75)</td>
<td>. .</td>
</tr>
<tr>
<td>&gt;5% Circulating Sézary cells</td>
<td>30 (97)</td>
<td>13 (81)</td>
<td>.07</td>
</tr>
<tr>
<td>Mean percentage Sézary cells</td>
<td>48</td>
<td>29</td>
<td>.17</td>
</tr>
<tr>
<td>Mean white blood cell count, % (normal, ≤11%)</td>
<td>13.8</td>
<td>8.4</td>
<td>.07</td>
</tr>
<tr>
<td>Mean lactic dehydrogenase level, U/L (normal, ≤620 U/L)</td>
<td>413</td>
<td>412</td>
<td>.99</td>
</tr>
<tr>
<td>Mean CD4+/CD8+ ratio (normal, ≤2)</td>
<td>21.9</td>
<td>3.3</td>
<td>.006</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number (percentage) of patients.

### Table 5. Types of Immunomodulatory Therapy Incorporated Into Patient Care

<table>
<thead>
<tr>
<th>Systemic Immunomodulatory Therapy</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracorporeal photopheresis</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Interferon alfa</td>
<td>30 (64)</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sargramostim</td>
<td>15 (32)</td>
</tr>
<tr>
<td>Retinoids</td>
<td>21 (45)</td>
</tr>
</tbody>
</table>

### Table 6. Clinical Response to Therapy of All 47 Patients

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Partial (≥50% disease clearance)</td>
<td>25 (53)</td>
</tr>
<tr>
<td>Total</td>
<td>37 (79)</td>
</tr>
<tr>
<td>No response (≤50% disease clearance)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Progression</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

### Table 7. Clinical Response by Therapeutic Group*

<table>
<thead>
<tr>
<th>Response</th>
<th>Combination Therapy (n = 31)</th>
<th>Photopheresis Monotherapy (n = 16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>6 (19)</td>
<td>6 (38)</td>
<td>. .</td>
</tr>
<tr>
<td>Partial</td>
<td>20 (65)</td>
<td>6 (38)</td>
<td>. .</td>
</tr>
<tr>
<td>Total</td>
<td>26 (84)</td>
<td>12 (75)</td>
<td>.47</td>
</tr>
<tr>
<td>No response</td>
<td>4 (13)</td>
<td>3 (19)</td>
<td>. .</td>
</tr>
<tr>
<td>Progression</td>
<td>1 (3)</td>
<td>1 (6)</td>
<td>. .</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number (percentage) of patients.
cytokine production by peripheral blood mononuclear cells in vitro.33 Because little is known about the use of multiple immunomodulatory agents to treat patients with advanced CTCL, our purpose was to determine the efficacy of this therapeutic approach.

Our previous experience formed the basis for the development of a clinical profile of those CTCL patients most likely to respond to extracorporeal photopheresis monotherapy. These clinical criteria include the presence of modest numbers of peripheral blood Sézary cells (10%-20% of mononuclear cells); short duration of disease (less than 2 years); normal or nearly normal numbers of cytotoxic T lymphocytes with nearly normal CD4+/CD8+ ratios; normal or modestly elevated WBC; no history of intensive chemotherapy; and absence of bulky lymphadenopathy or overt visceral disease.20,34 Using these criteria as a guideline, the patients who received combination biologic response therapy in the present study had a worse prognosis at the time of treatment initiation than those who received photopheresis monotherapy, as evidenced by higher CD4+/CD8+ ratios, higher WBCs, a higher percentage of patients with peripheral blood involvement by Sézary cells, and higher percentages of circulating Sézary cells than those who received photopheresis monotherapy. Although the differences in some of these parameters were not statistically significant, a 4-fold increase in sample size would be needed to achieve an 80% chance of detecting statistical significance. Therefore, we consider the finding of a higher number of poor prognostic factors in the population receiving multimodality immunomodulatory therapy clinically relevant.

For all 47 patients, the overall positive response rate, including complete and partial responders, was 79%. The positive response rate for the 31 patients who received combination therapy was 84%. Although some groups have reported response rates of 76% to 80% with photopheresis monotherapy, these rates were achieved in patient populations with more limited skin disease and/or normal WBCs and CD4+/CD8+ ratios.20,22 As most of our patients had multiple poor prognostic factors at the time of treatment initiation, it seems that multimodality biologic response therapy enhances clinical response in patients with an expected worse outcome. In addition, the median survival in our patient population, 68% of whom had stage III or IV CTCL, was 6.2 years. This represents a marked improvement in survival over historical controls, who had median survival times of 4.6 and 1.1 years for stages III and IV, respectively.6 Unfortunately, patients with extensive cutaneous tumors experienced poor responses to photopheresis alone or in combination with other immunomodulatory agents.

Survival curves were also calculated to compare survival between patients with limited skin disease and extensive disease. Patients with stages III and IV disease experienced a median survival of 4.6 years, whereas patients with early-stage disease had a median survival of 7.7 years. Nearly all of the patients in our study had peripheral blood involvement, which confers a worse prognosis in any stage of disease. Therefore, our patients with widespread disease experienced a marked improvement in survival over the previously reported median survival of 2.6 years for patients with erythrodermic CTCL and peripheral blood involvement who received PUVA, radiation therapy, or chemotherapy, alone or in combination.6 Additionally, Kim et al4 have found that age at presentation of 65 years or older, clinical stage of IV, and B stage of I are associated with poor prognosis.4 In their study, patients receiving traditional non-immunomodulatory therapy were categorized based on the number of poor prognostic factors present at the time of diagnosis. The median survival was 1.5 years for patients who presented with 2 or 3 poor prognostic factors, and 3.7 years for those who presented with 1 factor.4 The average
age of presentation for our patients was 62 years, and nearly all had peripheral blood involvement, independent of tumor stage. Thus, since most of our patients had 2 poor prognostic factors independent of tumor stage, treatment with combination biologic response therapy markedly improved survival in all our patients over that of historical controls with similar factors.

We compared survival between patients treated with multimodality immunostimulatory therapy and those who received extracorporeal photopheresis monotherapy to evaluate for a possible improvement in outcome with the addition of immunomodulatory agents. The median survival for the patients undergoing combination therapy was 6.2 years, whereas the median survival for the monotherapy group was 5.5 years. Although neither the differences between the median survival values nor the differences between the 2 survival curves were statistically significant, there may be a trend toward longer survival in patients treated with combination immunomodulatory therapy. Importantly, the patients who received combination immunomodulatory therapy had a worse prognosis at initiation of therapy. Therefore, the findings presented here suggest that multimodality biologic response therapy may be more effective for patients with multiple poor prognostic factors than extracorporeal photopheresis monotherapy.

The review of our experience with combination immunomodulatory therapy suggests that patients with advanced CTCL receiving this therapy experience equal or improved clinical outcomes when compared with historical controls. In comparison with patients with less severe disease treated with photopheresis monotherapy, patients with multiple poor prognostic factors experience equal or improved clinical outcomes when treated with multimodality immunostimululatory therapy. Although further investigation is needed to better establish the effectiveness of multimodality biologic response therapy for the treatment of cutaneous T-cell lymphoma, the results of our study suggest that it should be considered first-line therapy for patients with advanced-stage disease and multiple poor prognostic variables.

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