High Clinical Response Rate of Sézary Syndrome to Immunomodulatory Therapies

Prognostic Markers of Response

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Objectives: To quantify response rates of Sézary syndrome (SS) to multimodality immunomodulatory therapy and to identify the important prognostic parameters that affect overall response to treatment.

Design: Retrospective cohort study.

Setting: Cutaneous T-cell lymphoma clinic at The Hospital at the University of Pennsylvania.

Participants: Ninety-eight patients who met the revised International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) criteria for the diagnosis of SS and were seen over a 25-year period at the University of Pennsylvania.

Intervention: Patients were treated with at least 3 months of extracorporeal photopheresis and 1 or more systemic immunostimulatory agents.

Main Outcome Measures: Overall response to treatment was the main measurement of outcome.

Results: A total of 73 patients had significant improvement with multimodality therapy: 30% had complete response, with clearing of all disease (n=29), and 45% had partial response (n=44). At baseline, the complete response group had a lower CD4/CD8 ratio than the nonresponse group (13.2 vs 44.2) (P=.04) and a lower median percentage of CD4+/CD26− cells (27.4% vs 57.2%) (P=.01) and CD4+/CD7− cells (20.0% vs 41.3%) (P=.01). Median monocyte percentage at baseline was higher for patients who had a complete response than for nonresponders (9.5% vs 7.3%) (P=.02). The partial response group did not have any statistically significant variables compared with the nonresponse group.

Conclusions: In this large cohort study of patients with SS, a high clinical response rate was achieved using multiple immunomodulatory therapies. A lower CD4/CD8 ratio, a higher percentage of monocytes, and lower numbers of circulating abnormal T cells at baseline were the strongest predictive factors for complete response compared with nonresponse and warrant further examination in a larger cohort.

Published online August 15, 2011.

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphoma that present in the skin. The most common CTCL variants are mycosis fungoides (MF), which presents as patches, plaques, and tumors, and Sézary syndrome (SS), a leukemic form of CTCL. The annual incidence for MF and SS combined is estimated at between 3 and 9 cases per million people.1-3 Mycosis fungoides and SS are characterized by a proliferation of CD4+ type 2 helper T (T_h2) cells that inhibit the T_h1 response resulting in dysregulation of the immune system. These abnormal cells are currently detected by peripheral blood flow cytometry and lack CD26 or CD7 antigens.

Patients with SS present with erythroderma, a clonal T-cell proliferation in the peripheral blood, and a high frequency of pruritus. As the disease progresses, there is an amplified tumor burden represented by increased malignant T cells in the peripheral blood, lymph node enlargements, and visceral organ involvement. Sézary syndrome carries a poor prognosis, with a median survival of approximately 40 months after diagnosis4 and a 5-year survival rate as low as 30%.5

Earlier literature has reported that the prognosis for patients with MF or SS is dependent on stage, which is determined by

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the extent and type of skin lesions and extracutaneous involvement. In an effort to improve the accuracy of determining prognosis, the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) has recommended a revision of the classification and staging system to include skin, nodal changes, metastases, and blood involvement. Recently, it has been suggested that other factors may significantly influence prognosis. Studies have indicated that baseline serum lactate dehydrogenase (LDH) levels, age at diagnosis, Sézary cell count, white blood cell (WBC) count, prior exposure to multiple systemic drugs, tumor burden, and lymphadenopathy are strong predictors of prognosis in patients with erythrodermic CTCL.

Although the peripheral blood tumor burden often limits treatment for SS, there are currently multiple options for treating these patients. The therapeutic armamentarium includes extracorporeal photopheresis (ECP), interferons, retinoids, methotrexate, denileukin diftitox, histone deacetylase inhibitors, granulocyte-macrophage colony stimulating factor (GM-CSF), monoclonal antibodies, single- and multiple-agent chemotherapy, and adjuvant skin-directed therapies such as phototherapy and radiation therapy. The mean response rate for patients with CTCL treated with ECP is 63%, with 20% of patients experiencing a complete response (CR). Although there is currently no uniform standard of therapy for SS, preservation of the immune response through the use of ECP and biologic therapies is associated with high response rates that are considered more durable than those achieved with systemic chemotherapy. The purpose of the present study is to identify prognostic parameters and investigate the response rate of patients with SS treated at our center during the past 25 years with immunomodulatory therapies and ECP.

METHODS

A database was compiled for 143 patients diagnosed as having CTCL who received treatment with ECP at the University of Pennsylvania between 1985 and 2009. Patients diagnosed with SS who received ECP with multimodality therapy were selected. Sézary syndrome was defined as erythroderma with peripheral blood tumor burden determined by either Sézary cell count or flow cytometry and stage IIIB to IVB determined by the 2007 classification proposed by ISCL. In all selected cases, patients presented with erythroderma (T4) and blood involvement with abnormal T cells (B1 or B2). All patients with B1 involvement had either a positive T-cell receptor gene rearrangement noted on polymerase chain reaction analysis or a CD4/CD8 ratio greater than 10 to 1. Peripheral blood involvement was determined by either 1-µm section analysis of formalin-fixed buffy coats or by flow cytometry assessment of circulating CD4+CD26- or CD4+CD7- T cells. Every patient received a full skin and lymph node examination by at least 1 member of the primary investigator research team to determine clinical stage. Multimodality therapy was defined as ECP and 1 or more systemic immunostimulatory agents (interferon alfa, interferon gamma, sargramostim [GM-CSF], or systemic retinoids) for at least 3 months. The standardized regimen for each patient included triple therapy that combined ECP with interferon alfa and a systemic retinoid. Patients with refractory disease or contraindications to either interferon alfa or the systemic retinoid received alternative therapy with ECP and either a retinoid alone, interferon alfa alone, or in the case of refractory disease, the addition of interferon gamma or GM-CSF or both.

A retrospective medical chart review was performed on these 98 patients by 2 of us (B.A.R. and A.H.R.) in a manner consistent with protocols approved by the institutional review board. Over 30 variables were analyzed for each patient, including patient characteristics such as demographic information, duration of illness, and treatment received both prior to ECP initiation and during ECP treatment; laboratory values including complete blood count, Sézary cell count, flow cytometry findings, and LDH levels; and the response to therapy. We used the Social Security index and the personal knowledge of one of us (A.H.R.) to determine living status and cause of death for each patient. Patients who showed no clinical or pathologic evidence of disease made up the CR group. Relapse was determined by medical chart review and the personal knowledge of one of us (A.B.C.). The time to treatment failure was categorized as shorter than 6 months, from 6 to 12 months, from 12 to 24 months, and greater than 24 months.

All causes of death were included, and the Kaplan-Meier technique was used to estimate survival. The t test was used to compare normal distributions, and the Kruskal-Wallis test was performed for distributions that were skewed. The prognostic variables were analyzed using univariate models. The statistical package used for analysis was Stata, version 10.1 (Stata-Corp, College Station, Texas).

RESULTS

Of the 143 patients we identified who had received ECP, 98 patients fulfilled our selection criteria. That is, (1) they had either stage IIIB to IVB disease; (2) the diagnosis of Sézary syndrome; and (3) they underwent treatment for at least 3 months with ECP plus at least 1 of the stimulatory agents (Table 1). There were 31 patients diagnosed as having stage IIIB disease, 35 with stage IVA1, 28 with stage IVA2, and 4 with stage IVB. The mean age at diagnosis for stage IIIB was 62.8 years; stage IVA1, 60.9 years; stage IVA2, 63.4 years; and stage IVB, 65.3 years. All patients had blood involvement, shown either by flow cytometry or with Sézary cell count performed on 1-µm sections of formalin-fixed buffy coats of peripheral blood. Ninety-five percent of the patients who had documented flow cytometry testing in our cohort had more than 5% CD4+/CD26- cells detected in their blood by flow cytometry at baseline (n = 93) while 90% of them had over 10% CD4+/CD26- cells at baseline (n = 88). Among the 98 patients, 29 (30%) experienced a CR, defined as complete clearance of skin, blood, and nodal involvement for at least 4 weeks. Forty-four patients (45%) experienced a partial response (PR), defined as greater than 50% but less than 100% clearance of both the skin lesions and blood involvement. Twenty-four patients (25%) showed either no response (NR), defined as less than 50% improvement of skin and blood involvement, or no improvement or progressive disease (PD). Of the total population analyzed, the male to female ratio was 2 to 1. The mean age at diagnosis was 62.4 years (range, 29-89 years). The median duration of ECP treatment was 21 months (interquartile range, 11-37), with 1 patient receiving 154 months of treatment. The starting treatment for each patient involved 2 consecutive days of ECP every 4 weeks.
The ECP regimen was modified according to the patients’ response to the treatment. At the start of our medical chart review, 52 patients had died (53%). Thirty of these patients died from their disease. We were unable to verify the cause of death for 11 patients. Other causes of death included cardiovascular disease (n=2), infection (n=2) and other malignancy (n=7). Additional characteristics for the patient population are summarized by outcome in Table 1.

All patients concomitantly received at least 3 months of ECP and another biologic therapy. Most patients received interferon alfa (n=87) and/or a retinoid (n=84). Thirty percent of the patients received the standardized regimen of triple therapy that included ECP, interferon alfa, and a systemic retinoid (n=29). Twenty-four patients had contraindications for the use of either interferon alfa or the systemic retinoid. These patients received GM-CSF or interferon gamma. Fifty-one patients initially had refractory disease, and multiple other immunomodulatory therapies including GM-CSF or interferon gamma were included in the regimen in addition to interferon alfa and a retinoid. The number of patients receiving each treatment is listed in Table 2.

Time to treatment failure was stratified, and a summary is provided in Table 3. Fourteen patients maintained their response for greater than 2 years; 23 maintained their response for 12 to 24 months; 9 maintained their response for 6 to 12 months; and 8 maintained their response for less than 6 months. A Kaplan-Meier survival curve was calculated to determine survival rates. The overall 5-year survival rate from date of diagnosis of our cohort was approximately 55%, with a median survival

### Table 1. Demographic Features According to Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population</th>
<th>CR</th>
<th>PR</th>
<th>NR/PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient total</td>
<td>98</td>
<td>29</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Male sex</td>
<td>59 (60)</td>
<td>20</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>31 (32)</td>
<td>10</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>IVA1</td>
<td>35 (36)</td>
<td>16</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>IVA2</td>
<td>28 (29)</td>
<td>3</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>IVB</td>
<td>4 (4)</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Improved on treatment</td>
<td>73</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CR</td>
<td>29</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PR</td>
<td>44</td>
<td>NA</td>
<td>44</td>
<td>NA</td>
</tr>
<tr>
<td>Age at diagnosis, mean (median), y</td>
<td>62.4 (62)</td>
<td>59.5 (59)</td>
<td>64.0 (65)</td>
<td>63.0 (62)</td>
</tr>
<tr>
<td>ECP treatments, mean (median)</td>
<td>27.9 (21)</td>
<td>27.0 (20)</td>
<td>35.5 (28)</td>
<td>15.6 (12)</td>
</tr>
<tr>
<td>Dead, No.</td>
<td>52</td>
<td>6</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Cause of death, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCL</td>
<td>30</td>
<td>3</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; NA, not applicable; NR/PD, nonresponse and progressive disease; PR, partial response.

#### Table 2. Treatments Received by Patients According to Outcome and Stage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stage</th>
<th>CR (n=29)</th>
<th>PR (n=44)</th>
<th>NR/PD (n=25)</th>
<th>IIIb (n=31)</th>
<th>IVA1 (n=35)</th>
<th>IVA2 (n=28)</th>
<th>IVB (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td></td>
<td>29 (100)</td>
<td>44 (100)</td>
<td>24 (100)</td>
<td>31 (100)</td>
<td>35 (100)</td>
<td>28 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Interferon alfa</td>
<td></td>
<td>27 (93)</td>
<td>40 (91)</td>
<td>20 (80)</td>
<td>29 (94)</td>
<td>30 (88)</td>
<td>26 (93)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td></td>
<td>7 (24)</td>
<td>16 (36)</td>
<td>17 (68)</td>
<td>9 (29)</td>
<td>15 (43)</td>
<td>15 (54)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>TSEB</td>
<td></td>
<td>4 (14)</td>
<td>11 (25)</td>
<td>9 (36)</td>
<td>10 (32)</td>
<td>6 (17)</td>
<td>7 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>PUVA</td>
<td></td>
<td>15 (52)</td>
<td>14 (32)</td>
<td>11 (44)</td>
<td>8 (26)</td>
<td>17 (49)</td>
<td>15 (54)</td>
<td>0</td>
</tr>
<tr>
<td>UV-B</td>
<td></td>
<td>3 (10)</td>
<td>4 (9)</td>
<td>2 (8)</td>
<td>3 (10)</td>
<td>4 (11)</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Chemo</td>
<td></td>
<td>0</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td>4 (14)</td>
<td>8 (18)</td>
<td>3 (12)</td>
<td>3 (10)</td>
<td>8 (23)</td>
<td>3 (11)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
<td>6 (21)</td>
<td>16 (36)</td>
<td>4 (16)</td>
<td>4 (13)</td>
<td>10 (29)</td>
<td>11 (39)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Retinoid</td>
<td></td>
<td>24 (83)</td>
<td>38 (86)</td>
<td>22 (88)</td>
<td>25 (81)</td>
<td>31 (89)</td>
<td>26 (93)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

Abbreviations: Chemo, chemotherapy; CR, complete response; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; GM-CSF, granulocyte macrophage colony stimulating factor; NR/PD, nonresponse and progressive disease; PR, partial response; PUVA, psoralen plus UV-A; TSEB, total skin electron beam.

All data are reported as number (percentage) of patients.
time of 65 months. The 5-year survival rate for stage IIIB cases was approximately 80%; for stage IVA1, 80%; for stage IVA2, approximately 76%; and for stage IVB, 0%. As shown in the Figure, we observed a significant survival difference between patients with stages IIIB, IVA1, and IVA2 when individually compared with stage IVB cases ($P < .01$ for all comparisons). The survival in cases of stage IVA1 disease compared with IVA2 was also significantly better ($P < .05$). All other comparisons were not statistically significant (IIIB vs IVA1, $P = .79$; IIB vs IVA2, $P = .08$). The median survival rate for patients with stage IVA1 disease was 12 years; stage IVA2, 7 years. The median survival for patients with stage IIIB disease could not be calculated because many patients are still living. The median survival of patients with stage IVB was 2 years.

**CR vs NR/PD**

We compared the CR subgroup with the combined NR/PD subgroup. When analyzing peripheral blood flow cytometry values for phenotypically abnormal T cells, we found that the CR subgroup had a lower mean baseline CD4+ /CD26− percentage and mean baseline CD4+/CD7− percentage than the NR/PD subgroup (27.4% vs 57.2% [P = .01] and 20.0% vs 41.3% [P < .01], respectively). The CD4/CD8 ratio was lower in the CR group (13.2 vs 44.2 [P = .04]). The difference in baseline peripheral blood monocyte percentage was also significant. The CR group had a mean monocyte percentage of 9.5% compared with 7.3% in the NR/PD group (P = .02). Although the mean age for the CR subgroup was younger than that of the NR/PD group, 59.5 vs 63.0 years, the difference was not significant (P = .22). Sex was also not a determining factor in response (P = .57). In previous literature, mean serum LDH levels, disease stage, WBC count, percentage of natural killer cells, and eosinophilia were suggested as possible predictive factors. Our study did not find any of these variables to be significantly different between the CR and NR subgroups. Differences in the baseline WBC counts and serum LDH levels were observed between the CR and NR/PD subgroups, and although these 2 variables were not statistically significant (P = .06 and P = .14, respectively), a trend of improvement was noted, and the CR subgroup had a lower WBC count and LDH level (95% confidence intervals, 6.4-9.8 x 10^9/L vs 8.7-14.8 x 10^9/L and 493-738 U/L vs 590-824 U/L, respectively). (To convert WBC count to x 10^9/L, multiply by 0.001; to convert LDH level to micromol/L per liter, multiply by 0.0167.)

**PR vs NR**

We also compared the PR population with the combined NR/PD group. The PR subgroup had a lower mean baseline CD4+/CD26− percentage and lower mean baseline CD4+/CD7− percentage (50.7% vs 57.2% and 36.4% vs 41.3%, respectively). However, these values did not reach statistical significance. We noticed a similar trend for LDH levels. The PR group had more than a 100-point lower mean baseline LDH level than did the NR/PD group (592 vs 707 U/L) (P = .16).

**COMMENT**

Patients with SS have a poor 5-year survival rate. It is, therefore, important to identify patients with a worse prognosis early in their course in an effort to treat their disease more aggressively. Thus, recognizing predictive factors in this patient population will assist in determining treatment options for individual patients.

To our knowledge, the present study is unique in that it includes only patients with stage IIIB to IVB SS treated with ECP and multimodality immunomodulatory therapy. Our study found that baseline CD4/CD8 ratio, percentage of CD4+/CD26− and CD4+/CD7− cells, and percentage of monocytes within the circulation are statistically correlated with response to therapy. Not surprisingly, those patients with a lower burden of disease had a higher response rate. Previous studies have commented on the
importance of Sézary cell count as a predictive factor. Since flow cytometry is becoming more accessible, it will be especially useful for acquiring accurate quantitative data on the presence of phenotypically abnormal T cells within the peripheral blood.

We describe for the first time to our knowledge a significant association between circulating monocyte percentage and clinical response to ECP and immunomodulatory therapy. A higher baseline monocyte percentage was a strong predictive factor for CR. This might be explained by the potential enhancement of antigen-presenting cell numbers, which could lead to the improved ability to process apoptotic tumor cells that result from photopheresis therapy. The increased numbers of antigen-presenting cells might also be associated with an amplification of monocyte-derived cytokines, including interleukin 12 (IL-12) and interferon alfa, which are critical for the generation of an antitumor response. Indeed, use of recombinant IL-12 and interferon alfa are known to have a beneficial effect in the treatment of CTCL.

Although there were no significant variables distinguishing the PR and the NR/PD subgroups, noticeable trends were observed. Similar to the CR group, the PR patients had lower CD4+CD26− and CD4+CD7− cell percentages. Previous studies have suggested the predictive importance of LDH levels for patients with CTCL. We observed that the PR group had a lower LDH level than did the NR/PD patients, but the difference was not statistically significant. These trends are not surprising because abnormal T-cell levels and LDH values are associated with peripheral blood tumor burden and cell turnover. The low power of our study likely accounts for the lack of significant clinical indicators between these 2 subgroups.

The patients with SS treated with multimodality therapy at our institution experienced an overall response comparable to, if not higher than, the overall response found in earlier studies (74.4% compared with 63%). Importantly, our patients experienced a CR rate similar to or better than the CR rate found in other studies (30% vs 20%). This response rate supports the findings of earlier studies that multimodality therapy is likely more effective than monotherapy. Our cohort also had a higher 5-year survival than recorded in the literature (55% vs 30%).

There are numerous possible reasons why multimodality therapy may be more effective and therefore should be used. First, immunomodulatory therapies, including interferons, are likely to enhance the ECP-induced antitumor immunity, including the effects of cytotoxic T cells and natural killer cells. Second, both interferon gamma and GM-CSF enhance antigen presentation and are likely to support improved processing and presentation of antigens related to ECP-induced tumor cell apoptosis. Third, since many of the therapeutic agents used in our study, including interferon alfa and retinoids, induce apoptosis differently, they may have synergistic effects in this regard. Finally, we have observed biochemical resistance to certain therapies used to treat CTCL, including hexabene. Use of a multimodality approach may help circumvent and prevent tumor cell resistance through the mediation of multiple modes of tumor cell death.

There were a few limitations to our study. The low power of our study and the selection criteria prevented us from performing a more extensive multivariate analysis. Since death certificates are not public records, cause of death was determined from contacting family members of the deceased or from recall by the research team. Although our clinic is considered one of the larger referral centers for SS, a single-institution bias still exists. Nevertheless, the patient population included in the cohort was not restricted geographically because treated patients were referred widely from throughout North America. Therefore, we expect our outcome to have good reliability. Finally, our study was a retrospective study and was constrained by data collection within the patients’ medical charts. To date there have been no reported prospective studies analyzing predictive factors, although some studies have advocated the use of disease severity scoring systems as a means for predicting prognosis independent of TNMB staging. The classification of MF and SS has been modified throughout the years. Patients who were seen more recently have received a more thorough workup including advanced imaging with computed tomographic (CT) and positron-emission tomography CT scans that were not available to patients seen in the earlier years. Therefore, the disease in patients seen more recently may be more accurately staged.

In conclusion, our institution experienced a comparable response rate with multimodality immunomodulatory therapy compared with previously reported studies analyzing this approach to treatment. We confirmed the previously reported finding that a higher peripheral blood tumor burden is associated with poor response. We also observed that a higher number of antigen-presenting cells is associated with a better outcome. This is consistent with the hypothesis that antigen-presenting cells are critical for the processing of the tumor cells that are induced to undergo apoptosis by ECP. Although ECP is now widely used for SS, there is no evidence suggesting which other treatments should be used in concert and no universal standard of treatment for patients with SS. With an improved understanding of prognostic factors, we can better predict the outcome for individual patients and tailor therapy to the aggressiveness of the disease. We should also consider including these prognostic indicators when determining the stage of CTCL.

Accepted for Publication: June 22, 2011.
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Author Contributions: Drs Raphael, Suchin, and Rook had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Raphael, Suchin, Kim, and Rook. Acquisition of data: Raphael, Suchin, Morrissey, Kim, Gardner, Evans, Intracaso, Samimi, and Rook. Analysis and interpretation of data: Raphael, Shin, Suchin, Morrissey, Vittorio, and Gelland.
Drafting of the manuscript: Raphael, Suchin, Morrissey, and Rook. Critical revision of the manuscript for important intellectual content: Shin, Morrissey, Vittorio, Kim, Gardner, Evans, Introcaso, Samimi, and Gelfand. Statistical analysis: Raphael, Shin, and Gelfand. Obtained funding: Rook. Administrative, technical, and material support: Suchin and Vittorio. Study supervision: Suchin, Evans, Introcaso, and Rook.

Financial Disclosure: Dr Kim is an investigator for Ten X Pharmaceuticals, Biocryst, Gloucster, Centocor, and Yaupon and a consultant for Eisai. Dr Rook is a consultant for Hy Bio Pharma and has lectured for Therakos. Additional Contributions: We are indebted to the rest of the Cutaneous T-Cell Lymphoma staff, including Barbara DeNardo, RN, William Macey, RN, MS, Patricia Raphael, Shin, Morrissey, and Gelfand.

REFERENCES


