The Stanford University Experience With Conventional-Dose, Total Skin Electron-Beam Therapy in the Treatment of Generalized Patch or Plaque (T2) and Tumor (T3) Mycosis Fungoides

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Objective: To review the Stanford University experience with total skin electron-beam therapy (TSEBT) of 30 Gy or greater as monotherapy in patients with mycosis fungoides (MF) and compare with subgroups receiving adjuvant nitrogen mustard (HN2), and further update our experience with repeated courses of TSEBT.

Design: Retrospective study.

Setting: Academic referral center, multidisciplinary clinic.

Patients: A total of 180 patients with MF treated from 1970 through 2007 with T2 MF (103 with generalized patch or plaque disease) or T3 MF (77 with tumor disease). Patients with extracutaneous disease were excluded.

Interventions: Total skin electron-beam therapy with or without adjuvant topical HN2.

Main Outcome Measure: Clinical response rate, freedom from relapse (FFR), overall survival (OS), and progression-free survival (PFS) after TSEBT.

Results: The overall response rate (ORR) was 100%; 60% of patients achieved a complete clinical response (patients with T2 MF=75%, those with T3 MF=47%). The 5- and 10-year OS rates of the entire cohort were 59% and 40%, respectively. There were no significant differences in FFR (P=.30 for T2 disease; P=.50 for T3 disease), PFS (P=.10 for T2 disease; P=.40 for T3 disease), or OS (P=.30 for T2 disease; P=.50 for T3 disease) between adjuvant HN2 and TSEBT monotherapy cohorts. The ORR was 100% in patients receiving a second course of TSEBT with median FFR of 6 months.

Conclusions: A TSEBT of 30 Gy or greater is highly effective in treating T2-T3 MF, with better outcomes in T2 disease. There was no clinical advantage to adjuvant HN2 as used in our cohort. Second courses of TSEBT are safe and efficacious and provide clinically meaningful palliation for select patients.

Arch Dermatol. 2011;147(5):561-567
of active agents such as adjuvants. Furthermore, there remains a lack of consensus among experts as to the proper definition and/or efficacy of traditional end points, such as overall survival (OS) and progression-free survival (PFS), in an indolent lymphoma such as MF.18,29

In this study, we updated Stanford’s long-term experience with conventional-dose TSEBT (ie, doses ≥30 Gy) by using an expanded cohort of patients with T2-T3 MF who had a longer follow-up than previously reported. We further discuss our experience with the use of adjuvant topical HN2. Finally, we discuss our updated experience with a second course of TSEBT administered following an initial conventional course.

**METHODS**

We used the comprehensive database from the Stanford Multidisciplinary Cutaneous Lymphoma Program to identify patients with MF who received TSEBT in the Department of Radiation Oncology from January 1, 1970, through January 1, 2007. The study protocol was reviewed and subsequently approved by Stanford University’s (Stanford, California) institutional review board. The initial evaluation of all patients at the start of TSEBT course included a comprehensive physical examination, appropriate imaging, complete blood cell count, and assessment of their blood smear for SS involvement when appropriate. When indicated, additional staging and diagnostic studies were obtained, including evaluation of T-cell receptor clonality via polymerase chain reaction, SS flow panel, lymph node biopsy specimen, bone marrow biopsy specimen, or other imaging studies. Based on this comprehensive evaluation, patients’ disease was staged according to the AJCC TNMB classification system discussed herein. Notably, the database did not encompass information to differentiate between generalized patch disease (T2a) and generalized plaque disease (T2b).

**Figure 1** is a flowchart demonstrating the design of this retrospective study. Included in the analysis were patients who had TNMB classified as T2-3 N0-1 M0 B0 disease at initiation of TSEBT course (ie, patients with T1- or T4-classified disease and/or lymph node, visceral, or leukemia involvement were excluded from the study cohort). Only patients who received a dose of 30 Gy or higher for their first course of TSEBT at Stanford University’s Department of Radiation Oncology during the time interval noted herein were evaluated. The TSEBT was administered using the 6 dual field technique, with a dose of 1.5 to 2 Gy per 2-day cycle. Most patients received a total dose of 36 Gy (range, 30-40 Gy), and local boost treatments (10-15 Gy) were often delivered to tumor lesions or thick plaques. Furthermore, “shadowed” areas of the body, including the top of the scalp, the perineum, soles of the feet, and inflammatory folds, were routinely supplemented with electrons or orthovoltage irradiation (median dosage, 20 Gy) to compensate for their underdosering during TSEBT.20

We further identified patients who received a second course of TSEBT. We limited our analysis to patients who had T2-T3 N0-1 M0 B0 disease at time of the initial TSEBT course and who had received their first course at a dose of 30 Gy or higher (standard dose).

Following completion of TSEBT, many patients were treated with topical HN2 as an adjuvant regimen. A subgroup analysis was performed in this cohort of patients; this analysis excluded those who received other therapies in combination with topical HN2. The adjuvant use of topical HN2 was described previously.18 In brief, patients were advised to apply topical HN2 formulated in aqueous solution until early 1980s and in Aquaphor ointment (Beiersdorf Inc, Wilton, Connecticut) thereafter to their entire cutaneous surface on a once-daily basis starting 4 to 8 weeks following completion of TSEBT, after resolution of acute radiation-
related skin reactions. The initial prescribed dose was 10 to 20 mg/dL, which was increased in concentration (ie, >20 mg/dL) and/or frequency (ie, 2-3 times daily) in cases of slowly resolving or refractory disease. The intended length of treatment for adjuvant use was 6 months in most cases.

Initial clinical responses were assessed using a global skin response approximately 4 to 6 weeks following completion of the TSEBT course, after the acute skin reactions of radiotherapy had subsided. Complete clinical response (CCR) was defined as clinical resolution of all cutaneous lesions of MF. Patients who had at least a 50% clearing of their cutaneous lesions over baseline were considered to have a partial response (PR), and those with less than 50% skin clearing were considered to have stable disease. Complete responders were considered to have relapsed at the time of biopsy-proven recurrence of disease or clinical evidence of relapse without histopathologic confirmation. Progression-free survival was calculated from the date of initiation of TSEBT until documented date of increase in clinical stage or T classification or death secondary to any cause. It was subsequently displayed as a Kaplan-Meier plot.

Overall survival was calculated from the date of initiation of TSEBT and displayed as a Kaplan-Meier plot. Differentials of actuarial curves were determined using the log-rank test. In complete responders, freedom from relapse (FFR) was calculated from the date of initiation of TSEBT until the date of documentation of disease relapse. Multivariate analysis, where appropriate, was conducted using a Cox proportional hazards model. Survival curves and FFR were then calculated for the 2 subgroups using methods already described.

RESULTS

PATIENT CHARACTERISTICS

One-hundred and eighty patients (110 males and 70 females) qualified for inclusion in this analysis, and of these, the cases of 74 patients have been previously reported.10,18 Of this cohort, 103 had T2 disease (55 had stage IB disease; 48 had stage IIA disease), and 77 had T3 (stage IIB) disease at initiation of TSEBT. The median age at initiation of TSEBT was 57 years (range, 19-86 years), and median time from diagnosis to treatment was 4 months (range, 0-304 months). The median follow-up time was 77 months (range, 6-434 months). Most patients underwent TSEBT as first-line therapy for their MF, but the range for the cohort included up to 9 prior treatments. Forty-three patients with T2 disease and 42 with T3 disease received adjuvant topical NH2 as described herein. The median duration of treatment with topical NH2 was 7 months. Fourteen patients (7 with T2 disease and 7 with T3 disease) underwent a subsequent course of TSEBT. The median interval between the first and second courses was 44 months (range, 9-95 months), and median follow-up time following the second course was 15 months (range, 2-192 months). Although a second course was initiated with the intention to complete a standard course (ie, ≥30 Gy), the dose in some patients was limited by acute toxicities or progressive visceral involvement. Five of the 14 patients received a dose of at least 30 Gy, with the median dose for the second course being 24 Gy (range, 10-36 Gy).

RESPONSE RATES AND FFR

Table 1 summarizes the important clinical outcomes of the study cohort. All patients had clinically significant responses to TSEBT (ie, ≥50% improvement in skin involvement) with 63% achieving CCR. The CCR rates for patients with T2 and T3 disease were 75% and 47%, respectively. Among complete responders, the FFR was significantly longer for patients with T2 disease (ie, stages IB and IIA) than for those with T3 disease (ie, stage IIB) (Figure 2). The median duration of response in complete responders was 29 months in patients with T2 disease and 9 months for those with T3 disease (P = .01). There was no significant difference in FFR between patients with stage IB disease and those with stage IIA disease (P = .60). Within each T classification there was no significant difference in FFR in the adjuvant HN2 subgroup when compared with the cohort treated with TSEBT monotherapy (P = .40 for T2 disease; P = .80 for T3 disease). In multivariate analysis, T2 classification and lower number of prior therapies were correlated with an improved FFR (P = .01 and P = .04, respectively), whereas age, sex, and time from diagnosis to initiation of TSEBT were not statistically correlated with improved FFR.

Table 2 summarizes important clinical outcomes of the multiple-course cohort. Within this group, all patients responded to the first TSEBT course (ie, ≥50% improvement in skin involvement), with 7 of 14 achieving a CCR. All patients also responded to the second course of treatment with 2 of 14 achieving a CCR.
OVERALL AND PFS

The 5-year and 10-year OS rates for the entire cohort were 63%, and 44%, respectively. Overall survival was significantly longer for patients with T2 disease than those with T3 disease (median OS: 10.9 years vs 4.7 years; \( P < .001 \)). Among the T2 group there was no significant difference in OS between patients with stage IB disease and those with stage IIA disease. Within each T classification, no significant differences were seen in OS when the adjuvant HN2 subgroup was compared with the TSEBT monotherapy cohort (\( P = .30 \) for T2 disease; \( P = .50 \) for T3 disease). Multivariate analysis identified T2 classification (\( P < .001 \)), younger age (\( P < .001 \), and lower number of prior treatment courses (\( P = .05 \)) as prognostic variables for improved OS. At the time of study analysis, 136 of the patients (75%) had died. Another 27 (15%) were alive with disease, and 17 (9%) were alive with no evidence of disease at their last follow-up assessment. Mycosis fungoides was the contributing factor in the deaths of 69 of the patients (51%).

As shown in Figure 3, similar trends were noted in PFS, with patients who had T2 disease enjoying significantly longer PFS than patients with T3 disease (median PFS, 8.5 years vs 2.9 years; \( P < .001 \)). There was no significant difference in PFS between patients with stage IB disease compared with those with stage IIA disease (\( P = .20 \)). Similarly, as in OS data, within each T class no significant difference in PFS in patients with stage IB disease compared with those with stage IIA disease (\( P = .20 \)). Similarly, as in OS data, within each T class no significant difference in PFS was noted between the adjuvant HN2 and TSEBT monotherapy subgroups (\( P = .10 \) for T2 disease; \( P = .40 \) for T3 disease). In multivariate analysis, only T2 class and limited number of prior treatments were found to be significantly correlated with improved PFS (\( P = .03 \) and \( P = .004 \), respectively).

Within the multiple course cohort, median PFS and OS were both 29 months (range for PFS, 3-192 months; range for OS, 3-189 months) following the second treatment course. Ten of the 14 had experienced disease progression between treatments. Of these, 5 had extracutaneous disease at the time of second treatment. The PFS for those with extracutaneous disease at the time of the second treatment was shorter than for those with disease limited to the skin (Kolmogorov-Smirnov test; \( P < .05 \)). Thirteen of the 14 patients had died at the time of this report; 11 of these died of causes directly related to MF, while 3 died of unrelated causes. For all 13 patients who died, the date of progression was defined as the date of death. To date, 1 patient is alive with disease 192 months following the second course of TSEBT, and the disease had not progressed at the time of the last follow-up.

TOXICITIES

Nearly all patients experienced mild to moderate radiation-induced dermatitis, partial or complete alopecia, nail dystrophy, and generalized xerosis. A small number of patients experienced radiation-induced milia and epidermal inclusion cysts. In most patients, radiation-associated toxicities were reversible, but the time to recovery was variable (\( \leq 2 \) years), and occasionally recovery was partial. Acute toxicities experienced during the second course of TSEBT were not qualitatively different than those experienced during first course but were often accentuated in severity. These acute toxicities included erythema, edema (especially of hands and feet), alopecia, and dry skin. Edema of the feet was the primary toxicity associated with decreased second-course dose. Long-term sequelae are difficult to attribute exclusively to TSEBT because all patients underwent other forms of skin-directed therapy (eg, topical HN2 or phototherapy) for recurrences subsequent to their TSEBT course; however, they included scattered telangiectasias, diffuse xerosis, pigmented changes, and, in the case of 1 patient, multiple pigmented basal cell carcinomas. These were qualitatively similar in patients who received a second course of TSEBT.

COMMENT

The selection of treatment for MF is largely dependent on the clinical stage. According to the National Comprehensive Cancer Network (NCCN) guidelines, the primary treatment of T1, T2, and limited T3 MF without B1 blood involvement or histologic evidence of folliculotropism or large-cell transformation (markers of more aggressive disease) involves administration of skin-directed therapy (eg, topical HN2 or phototherapy) for recurrences subsequent to their TSEBT course; however, they included scattered telangiectasias, diffuse xerosis, pigmented changes, and, in the case of 1 patient, multiple pigmented basal cell carcinomas. These were qualitatively similar in patients who received a second course of TSEBT.
Table 2. Clinical Outcomes of the Multiple-Course Cohort*

<table>
<thead>
<tr>
<th>T Class</th>
<th>TSEBT Course</th>
<th>CR</th>
<th>PR</th>
<th>OS, Median, mob</th>
</tr>
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<tbody>
<tr>
<td>T2 (8 patients)</td>
<td>First</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>45.5</td>
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<tr>
<td></td>
<td>Second</td>
<td>2 (25)</td>
<td>6 (75)</td>
<td></td>
</tr>
<tr>
<td>T3 (6 patients)</td>
<td>First</td>
<td>1 (17)</td>
<td>5 (83)</td>
<td>53.3</td>
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<tr>
<td></td>
<td>Second</td>
<td>0</td>
<td>6 (100)</td>
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Abbreviations: CR, complete response; OS, overall survival; PR, partial response; TSEBT, total skin electron-beam therapy.
* Calculated from the start of second course of TSEBT.
+ Data are given as number (percentage).

Our historical cohort of patients treated with total doses lower than 30 Gy we can confirm the superiority of high-dose TSEBT (CCR rates of 75% vs 41% for patients with T2 disease). However, our reported cutaneous remission rates are somewhat lower than the CCR rates of 80% or higher reported for patients with T2 disease and the CCR rates of 50% or higher reported for patients with T3 disease treated with conventional-dose TSEBT in some other large institutional case series. One possible explanation for this is that assignment of a CCR and T2-T3 staging may differ among institutions. Furthermore, we did not categorize our patients with T3 disease into “limited tumor” and “extensive tumor” subgroups. Quiros et al previously reported on the significant impact of the extent of skin involvement on CCR rates as well as DFS and OS in patients with T3 disease. This may account for the apparent lower-than-expected response rates in our cohort with T3 disease who may in general have had a more extensive tumorous disease than patients in other case series. Another factor to consider is proportion of patients with large cell transformed or folliculotropic disease, which are both predictors of worse prognosis and thus may be linked with lower response rates.

Patients with T2 disease in our cohort also experienced a significantly longer response duration (median duration, 29 months) than those with T3 disease (median duration, 9 months) following achievement of CCR to TSEBT (P = .006). Our data failed to show an improvement in FFR in complete responders treated with adjuvant topical HN2 compared with patients treated with TSEBT to a CR and simply observed over time (P > .40 for T2 disease; P > .80 for T3 disease). There were no significant differences in patient characteristics, including median age and prior number of therapies, between the 2 subgroups (data not shown). This finding is in contrast to our previously reported trend toward improvement in FFR with use of adjuvant HN2 compared with the observation group. Several factors associated with the composition of the 2 respective cohorts may contribute to this discrepancy. In the previous cohort, treated patients were within 4 months of diagnosis, and thus most, if not all, received TSEBT as initial therapy. Because our cohort included all T2- and T3-classified patients treated after 1970 with TSEBT, patients were more heavily pretreated (range of prior therapies, 1-9) than the historical cohort. In our multivariate analysis we noted both lower T class and prior number of therapies to be significantly correlated with improved FFR. Furthermore, the duration of therapy with adjuvant HN2 between the 2 cohorts differs significantly (median, 7.0 vs 16.5 months in the current and historical cohorts, respectively) and thus may contribute to the longer cutaneous remission in the prior cohort. As expected, patients with T2 disease had a significantly longer OS and DFS than those with T3 disease (median OS, 10.9 vs 4.7 years; P < .001). However, with a median follow-up of 6.4 years, the use of adjuvant HN2 did not confer an advantage in OS or DFS in either the T2 or T3 subgroups. Overall, our cohort is significantly larger in size (180 patients) compared with the historical cohort (82 patients) and includes more patients in the respective adjuvant HN2 subgroups (85 compared with 23). This increased power allows us to be more definitive in concluding that there is no significant clinical advantage to the use of adjuvant HN2 when used for an intended duration of 6 months in patients treated with high-dose TSEBT.

Multiple studies have investigated a variety of non-cytotoxic therapies as adjuvant to TSEBT. There are other studies examining the impact of chemotherapy (single or multiagent) as adjuvant therapy or in combination with TSEBT. However, chemotherapy is not currently considered to be an appropriate treatment for patients with skin-limited disease who have responded to other therapies. Therefore, we limit our discussion to studies investigating skin-directed or biologic/immunomodulating systemic agents used as adjuvant therapy following TSEBT.

Jones et al reported on the use of conventional-dose TSEBT (35 Gy) in combination with concurrent and adjuvant (6 months) oral etretinate in patients with T1 and T2 disease. Twenty-three patients were treated with the combination regimen, whereas 9 patients underwent radiotherapy only. While the combination treat-
ment was tolerable, there was no improvement in relapse-free survival compared with the control group at a median follow-up of 2 years. Quirós et al\textsuperscript{20} compared the outcomes of a historical cohort of 14 patients (6 with T1 disease, 8 with T2 disease) treated with TSEBT to 36 Gy followed by adjuvant psoralen–UV-A (PUVA) therapy with those receiving non-PUVA adjuvant or no adjuvant therapies following their TSEBT course. The phototherapy was initiated within 2 months of TSEBT, tapered over 3 to 6 months, and then continued monthly until there was clinical relapse. The authors reported an improvement in 5-year DFS in the subgroup receiving adjuvant PUVA therapy when compared with the cohort treated with TSEBT alone or in combination with other non-PUVA adjuvant therapies (85\% vs 50\%; \(P < .02\)). There was no significant improvement in 5-year OS between the subgroups. Within the subgroup receiving PUVA therapy, all patients experienced some degree of photo-related skin toxicities, which were deemed as acceptable. The major shortcoming of this retrospective study is that comparisons were made between different historical cohorts, and thus any comparative conclusions regarding the efficacy of PUVA as an adjuvant therapy are speculative. Furthermore, prolonged use of PUVA may increase risk for secondary cutaneous malignant diseases and may not be appropriate for this select group of patients.

Wilson et al\textsuperscript{26} retrospectively reviewed the outcome in 163 patients with T1-T4 disease treated with TSEBT to 36 Gy. A subgroup of patients who had achieved CCR or “good partial response” to TSEBT received either adjuvant extracorporeal photopheresis (ECP) (14 patients) or adjuvant systemic chemotherapy with doxorubicin/cyclophosphamide (83 patients). The authors reported a trend toward improved OS in the adjuvant ECP subgroup compared with the no-adjuvant subgroup (\(P < .06\)) for patients with T3 or T4 disease. There was no statistically significant improvement in OS with adjuvant chemotherapy. No benefit in OS was noted in the cohort with T1-T2 disease with the addition of either adjuvant therapy, which also provided no benefit in relapse-free survival for all T classes. Again, despite the observed trend toward improved OS, no definitive conclusions could be made about the role of ECP owing to the small sample size (14 patients) and the retrospective nature of the study. Furthermore, selection bias may have been a factor in observed differences in OS because patients were offered adjuvant therapy based on their response to TSEBT. In a later retrospective series by the same authors,\textsuperscript{25} the impact of concomitant and/or adjuvant ECP was analyzed in 44 patients with erythrodermic MF (ie, stages III and IV) treated with TSEBT at 32 to 40 Gy. The authors reported significant improvement in DFS and cause-specific survival in the subgroup of patients treated with TSEBT and ECP compared with the subgroup treated with TSEBT alone. Again, toxicities were consistent with what would be expected for the individual treatment modalities.

In 2007, Roberge et al\textsuperscript{13} reported on the impact of interferon alfa-2b used as an adjuvant regimen in patients with stage IA-IVA disease treated with TSEBT to a median dose of 35 Gy. Of the 50 patients evaluated, 31 were treated with TSEBT alone and 19 with TSEBT plus interferon alfa-2b. Interferon was administered subcutaneously at a dose of \(3 \times 10^6\) U 3 times weekly starting 2 weeks prior to TSEBT, continued concurrently with radiotherapy, and then for an additional 12 months following TSEBT. No significant improvement in CR rate, DFS, or OS was noted with the addition of interferon even after controlling for disease stage. The authors noted that routine use of concurrent interferon was no longer followed at their institution due to these results.\textsuperscript{23}

In this report, we also have provided an update on our experience with patients who have received multiple courses of TSEBT,\textsuperscript{29} adding several patients treated with a second course of TSEBT since the prior publication but excluding those who did not receive an initial standard dose or who had extracutaneous disease at first treatment. In general, the criteria used for selection of patients for a second course of TSEBT at our institution included the following: (1) refractory to other treatment modalities with progressive disease, (2) a good response and tolerance to the first course of TSEBT, and (3) an adequate interval between the first and second courses in order to reduce cumulative radiation-induced toxicity. Overall, the second-course data demonstrate that TSEBT can be effectively used for palliation of skin symptoms in patients with disease that is stable or has progressed following the first treatment. All patients achieved cutaneous response to treatment, even in the presence of extracutaneous disease at the time of second treatment. Although acute toxicity required a lower treatment dose at the time of the second treatment in several patients, long-term toxicities were not different than those seen following the first course of therapy.

Similar outcomes were reported by Wilson et al,\textsuperscript{37} who described 14 patients with MF who received at least 2 courses, 5 of whom received a third course. Of these 14 patients, 10 had T2 or T3 disease and had received a standard dose at first treatment. Nine patients achieved CR to first treatment, with a median disease-free interval of 9 months (range, 6-132 months). Eight of the 10 achieved CR to the second treatment, with a median disease-free interval of 11.5 months (range, 1-27 months).

In summary, our data support the use of high-dose TSEBT as the most effective treatment modality for initial or relapsed T2 and T3 MF as evidenced by the overall response rate of 100\% and high likelihood of effective palliation. However, because several novel systemic agents have become available over the past decade, the use of TSEBT has become increasingly reserved for treatment of relapsed or refractory disease. As expected, the clinical outcomes, including CR rate, FFR, PFS, and OS, were significantly better for patients with T2 vs T3 disease. Our findings do not support the routine use of adjuvant topical HN2 in complete responders if used for an intended length of treatment of 6 months. However, previously we showed a trend toward improved response duration with longer use of adjuvant HN2 (median duration, 16.5 months). In our current practice we use topical HN2 routinely in patients who have near-complete cutaneous response because it facilitates further resolution of residual disease as well as provision of emoliation. As discussed herein, the findings of studies investigating the efficacy of adjuvant agents after TSEBT are mixed. Because an improved quality of life is an important goal of all adjuvant therapies, the use of skin-directed treatments that prolong cutaneous remission needs to be further investigated. Future studies, for instance, may
analyze different concentrations and treatment frequencies of HN2 and phototherapy that may maximize response duration (and hence quality of life) while minimizing toxicities. In addition, novel biologic agents are becoming available that deserve to be tested in the adjuvant setting. Future investigations should further be geared toward careful prospective assessment of the different adjuvant agents, using well-defined end points, potentially as multi-institutional studies. Until such studies are undertaken and completed, the guidelines of consensus groups such as the NCCN and EORTC remain helpful in selecting therapy for the patients with MF.

Accepted for Publication: October 4, 2011.

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Author Contributions: Drs Navi and Kim 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.

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Acquisition of data: Navi, Riaz, Levin, Sullivan, Kim, and Hoppe.

Analysis and interpretation of data: Navi, Riaz, Levin, Kim, and Hoppe.

Drafting of the manuscript: Navi, Riaz, Levin, Sullivan, and Kim.

Critical revision of the manuscript for important intellectual content: Navi, Riaz, Kim, and Hoppe.

Statistical analysis: Riaz and Kim.

Obtained funding: Kim and Hoppe.

Administrative, technical, and material support: Navi, Sullivan, Kim, and Hoppe.

Study supervision: Kim and Hoppe.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by the Stanford Cutaneous Lymphoma Research Fund.

Additional Contributions: Sam Brain, PhD, and Carol Bruce, BS, assisted with medical chart and data collection.

REFERENCES