

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

Daniel Navi, MD; Nadeem Riaz, MD; Yakir S. Levin, MD, PhD; Naomi C. Sullivan, BS; Youn H. Kim, MD; Richard T. Hoppe, MD

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.

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MYCOSIS FUNGOIDES (MF) is an extranodal non-Hodgkin lymphoma of CD4⁺ T-cell origin with primary cutaneous involvement. It is the most common subtype of primary cutaneous T-cell lymphoma with an overall incidence of 6.4 per 1 000 000 persons in the United States and peak age at presentation of 55 to 60 years.¹⁻³ The cutaneous presentations of MF are heterogeneous: pruritic patches and plaques characterize the early stages of the disease, whereas more advanced stages manifest with cutaneous tumors or erythroderma. Sézary syndrome (SS) is a leukemic variant of MF typically seen in patients with an erythrodermic presentation and usually with associated generalized lymphadenopathy.⁴

The staging of MF is based on a tumor-node-metastasis-blood (TNMB) classifica-

tion system proposed by the American Joint Committee on Cancer (AJCC), which incorporates the morphologic characteristics and extent of skin lesions (T), lymph node status (N), extracutaneous disease (M), and leukemic involvement (B).⁵ The prognosis of MF is related directly to the clinical stage at diagnosis, with the most predictive factors being patient age, T classification, and presence of extracutaneous disease.⁶ The therapeutic options for MF and SS include a broad spectrum of modalities encompassing skin-directed therapies for early-stage disease and systemic therapies for more advanced stages. The selection of a specific treatment regimen is made primarily on the basis of a patient's clinical stage, and as such, consensus guidelines have been proposed for stage-adapted treatment of MF/SS.^{7,8} Despite the wide spectrum of available therapeutic options, MF remains largely an incurable dis-

Author Affiliations: Departments of Dermatology (Drs Navi, Levin, and Kim) and Radiation Oncology (Drs Riaz and Hoppe), Stanford Cancer Center, Stanford University, Stanford, California; and Department of Biological Sciences, Vanderbilt University, Nashville, Tennessee (Ms Sullivan).

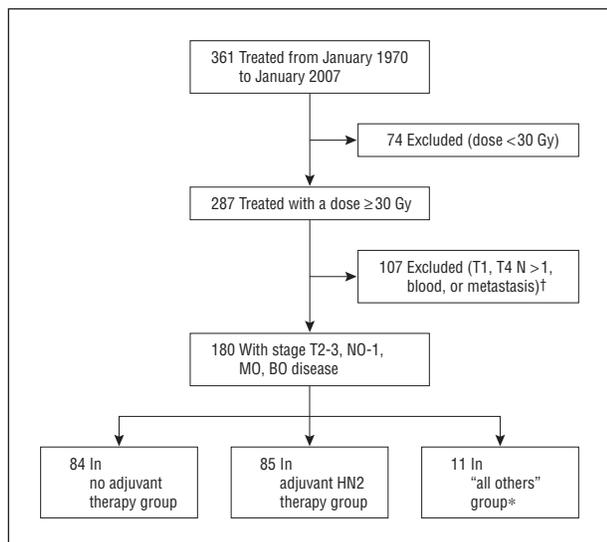


Figure 1. Study design. *"All others" includes patients who received adjuvant therapy, other than adjuvant topical nitrogen mustard (HN2), in conjunction with total skin electron-beam therapy (TSEBT). These patients were not included in a subgroup analysis comparing the effectiveness of adjuvant HN2 vs TSEBT alone. †Patients with T1- or T4-classified disease and/or lymph node, visceral, or leukemic involvement were excluded from the study cohort.

ease. The main goals of current treatment strategies are thus to provide palliation of symptoms and potentially decrease the risk of extracutaneous spread.⁷

Total skin electron-beam therapy (TSEBT) involves the administration of ionizing radiation to the entire skin surface. While it has been used in the treatment of MF since 1951,⁹ major advances have been made over the past several decades in both our understanding of the radiobiology as well as the technical aspects of this treatment modality.¹⁰⁻¹² Electron-beam irradiation is more penetrating than other skin-directed treatments (eg, topical nitrogen mustard [HN2] or phototherapy) and is thus generally considered a reasonable initial therapy for patients with T2-classified (ie, generalized patch or plaque) and T3-classified (ie, tumorous) disease.^{13,14} The efficacy of TSEBT in erythrodermic MF (ie, T4 disease) is more controversial, with opposing recommendations coming from major institutions based on their cumulative experience.¹⁵⁻¹⁷

Several retrospective reviews of large clinical cohorts over the past 2 decades have consistently demonstrated the efficacy of high-dose (≥ 30 Gy) TSEBT in producing high clinical response rates.^{10,18-20} Both Jones et al¹⁰ and Chinn et al¹⁸ previously reported on the comprehensive database of Stanford Multidisciplinary Cutaneous Lymphoma Program used in this study. More recently the European Organisation for Research and Treatment of Cancer (EORTC)²¹ has published consensus guidelines for optimal delivery of TSEBT, which is supported by these retrospective studies. Despite advances in optimization of this modality leading to significant improvement in response outcomes, the major shortcoming of TSEBT remains its duration of response.^{6,22} Given that recurrence of disease is the norm in patients achieving clinical responses to TSEBT, a variety of agents known to be active in MF have been used as adjuvant or maintenance therapies.^{18,20,23-27} The outcomes of these studies are mixed, and thus to date there has been no consensus on the role

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.^{28,29}

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 system⁵ discussed herein.⁵ 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 leukemic 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.³⁰ 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 inframammary folds, were routinely supplemented with electrons or orthovoltage irradiation (median dosage, 20 Gy) to compensate for their underdosing during TSEBT.³⁰

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-

Table 1. Clinical Response and Outcomes of Cohort

Type of Therapy (No. of Patients)	Median Follow-up, y	No. (%)		Median, y		
		CCR	PR	OS	PFS	FFR
T2 class						
27 Received TSEBT monotherapy	13.0	41 (72)	16 (28)	11.3	8.9	2.4
43 Received TSEBT + HN2	8.9	33 (77)	10 (23)	10.9	8.5	2.7
Total of 103 patients with T2 disease ^a	11.7	77 (75)	26 (25)	10.9	8.5	2.4
T3 class						
27 Received TSEBT monotherapy	5.5	12 (44)	15 (56)	4.2	1.8	1.0
42 Received TSEBT + HN2	4.6	20 (48)	22 (52)	3.9	2.9	0.8
Total of 77 patients with T3 disease ^a	5.2	36 (47)	41 (53)	4.7	2.9	0.8

Abbreviations: CCR, complete clinical response; FFR, freedom from relapse; HN2, adjuvant nitrogen mustard; OS, overall survival; PFS, progression-free survival; PR, partial response; TSEBT, total skin electron-beam therapy.

^aAll patients with T3 disease and all of those with T2 disease include patients who received adjuvant therapy, other than HN2, in conjunction with TSEBT. See Figure 1 for details of study groups.

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 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. Differences in 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.

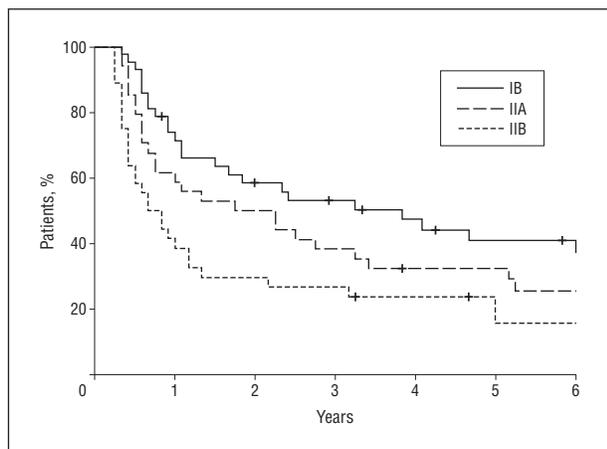


Figure 2. Freedom from relapse (FFR) by disease stage. Patients with stage IB disease (n=43) and stage IIA disease (n=34) who had a complete clinical response (CCR) to total skin electron-beam therapy had significantly higher FFR rates than those with stage IIB (n=36) with CCR ($P=.01$). There was no difference in FFR between the patients with stage IB disease and those with stage IIA disease ($P=.17$).

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 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 treat-

ment 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 (≤ 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, pigmentary 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, selected based on the extent and type of skin involvement. Among these therapies, TSEBT is a well-established modality with multiple large institutional case series reporting its high efficacy rate when used either for initial or relapsed disease.¹⁸⁻²⁰ Since there are only a few randomized studies comparing radiation therapy with other therapeutic regimens,³¹ institutional experience and patient preference largely guide treatment selection. At Stanford Cancer Center, TSEBT is routinely considered as primary therapy for patients with extensive thick plaques (T2) or tumor disease (T3). These are mostly patients with rapidly progressive disease or those who have failed attempts at disease control with other skin-directed and/or systemic agents.¹³ The efficacy of conventional-dose TSEBT (ie, total doses ≥ 30 Gy) in producing superior CR and FFR rates has been well established.^{32,33}

Our data confirm that conventional-dose TSEBT is significantly more efficacious in T2 than T3 MF (CCR rates of 75% vs 47%; $P < .001$). Furthermore, when compared with

Table 2. Clinical Outcomes of the Multiple-Course Cohort^a

T Class	TSEBT Course	CR	PR	OS, Median, mo ^b
T2 (8 patients)	First	6 (75)	2 (25)	45.5
	Second	2 (25)	6 (75)	
T3 (6 patients)	First	1 (17)	5 (83)	53.3
	Second	0	6 (100)	

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; TSEBT, total skin electron-beam therapy.

^aCalculated from the start of second course of TSEBT.

^bData 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).³⁴ However, our reported cutaneous remission rates are somewhat lower than the CCR rates of 80% or higher reported for patients with T2 disease^{19,20} and the CCR rates of 50% or higher reported for patients with T3 disease³⁵ 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. Quirós et al³⁵ previously reported on the significant impact of the extent of skin involvement on CCR rates as well as DFS and OSS 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.¹⁸ 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

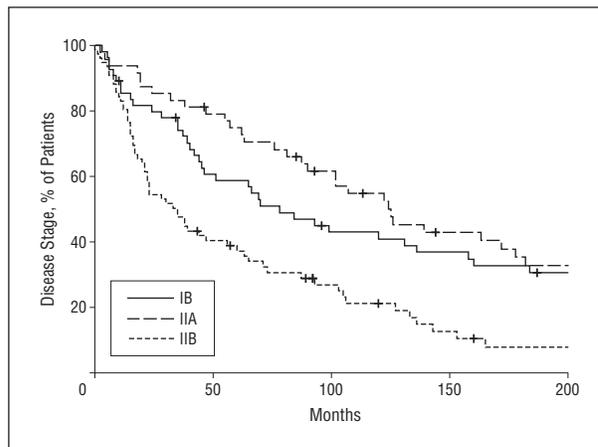


Figure 3. Progression-free survival by disease stage. Median lengths of progression-free survival for patients with stage IB disease ($n = 55$), stage IIA disease ($n = 48$), and stage IIB disease ($n = 77$) are 6.5, 10.4, and 2.9 years, respectively. Progression-free survival was significantly longer for those with stage IB/IIA disease vs those with stage IIB disease ($P \leq .001$). There was no difference between stage IB disease and stage IIA disease ($P = .21$).

disease had a significantly longer OS and PFS 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 PFS 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 al²⁴ 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 al²⁰ 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 al²⁶ 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 photochemotherapy (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 addition of 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,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 al²³ 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 3×10^6 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.²³

In this report, we also have provided an update on our experience with patients who have received multiple courses of TSEBT,³⁶ 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,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 emolliation. 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.

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Correspondence: Daniel Navi, MD, Department of Dermatology, Stanford University, 450 Broadway St, Pavilion B, Redwood City, CA 94063 (dnavi@stanford.edu).

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