Maintenance Therapy for Cutaneous T-cell Lymphoma After Total Skin Electron Irradiation: Evidence for Improved Overall Survival With Ultraviolet Therapy

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Abstract

We assessed the impact of maintenance therapy following total skin electron beam therapy (TSEB) in 101 cutaneous T-cell lymphoma (CTCL) patients in a single-center retrospective analysis. Maintenance regimens included ultraviolet, nitrogen mustard, and systemic therapies. Any maintenance was associated with longer progression-free survival (PFS) compared to no maintenance, while ultraviolet-based maintenance improved both PFS and overall survival, supporting maintenance administration following TSEB in CTCL.

Background: Treatment of cutaneous T-cell lymphoma (CTCL) with total skin electron beam (TSEB) therapy has been associated with deep responses but short progression-free intervals. Maintenance therapy might prolong the response duration; however, limited data assessing the outcomes with maintenance therapy after TSEB are available. We evaluated the effect of maintenance therapy on the outcomes for patients with CTCL receiving TSEB therapy. **Materials and Methods:** We conducted a single-center retrospective analysis of 101 patients with CTCL who had received TSEB therapy from 1998 to 2018 at the Winship Cancer Institute of Emory University and compared the overall survival (OS) and progression-free survival (PFS) for patients had received maintenance therapy, including retinoids, interferon, ultraviolet therapy, nitrogen mustard, and extracorporeal photopheresis compared with those who had not. **Results:** We found that pooled maintenance therapies improved PFS (hazard ratio [HR], 0.60; $P = .026$) but not OS (median HR, 0.73; $P = .264$). The median PFS and OS was 7.2 months versus 9.6 months and 2.4 years versus 4.2 years for the no maintenance and maintenance groups, respectively. On exploratory analysis of the individual regimens, ultraviolet therapy was associated with improved OS (HR, 0.21; $P = .034$) and PFS (HR, 0.26; $P = .002$) compared with no maintenance. **Conclusion:** Among the patients with CTCL who had received TSEB therapy, maintenance therapy improved PFS for all patients, and ultraviolet-based maintenance improved both PFS and OS in a subset of patients.

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Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare non-Hodgkin lymphoma that originates from skin-homing T lymphocytes. Although most patients present with early-stage disease (stage IA-IIA) and are likely to experience a favorable prognosis, advanced-stage disease (stage IIB-IVB) has been associated with inferior outcomes and a median survival of 2 to 5 years.[1,2]

Total skin electron beam (TSEB) is a well-established treatment modality for advanced CTCL and has been associated with a near 100% response rate in the skin, with most achieving a complete response (CR) when delivered at conventional doses.[3-5] TSEB can be used as an individual regimen or as part of a conditioning regimen in total body irradiation for allogeneic hematopoietic stem cell transplantation.[6] Although initial studies demonstrated that high-dose or conventional-dose (~36 Gy) TSEB resulted in better response rates and durations of response compared with low-dose TSEB (~12 Gy), low-dose TSEB has emerged as an acceptable approach to control disease symptoms with reduced toxicity, enabling repeat administration.[3,5,7-10] Our group has piloted additional techniques to treat CTCL such as using a dual-field rotational technique, which has further improved the skin responses.[11] However, in the absence of additional therapy, Progression-free survival (PFS) can be as poor as 3 months, especially with low-dose TSEB for patients with advanced disease.[12] TSEB can be augmented with maintenance therapy, including skin-directed and systemic therapies. However, the utility of maintenance therapy has remained unclear owing to the limited data available in this setting.[13-15] For early-stage disease, psoralen and ultraviolet (UV) A (PUVA) and topical nitrogen mustard (NM) maintenance has demonstrated improvements in DFS but not OS compared with no maintenance.[14,16] However, conflicting data have been reported regarding the benefit of systemic maintenance therapy after TSEB in patients with advanced-stage disease.[13,16-18] We assessed the effect of maintenance therapy on outcomes for patients with CTCL treated with TSEB at our institution in a retrospective cohort.

Materials and Methods

Patients

We conducted a single-center retrospective analysis at the Winship Cancer Institute of Emory University. A total of 101 patients with CTCL who had received TSEB from 1998 to 2018 were included in our analysis. No CTCL subtypes were excluded. The patients who had received TSEB were selected from an existing cutaneous lymphoma database and cross-referenced with a list of patients obtained from the Emory Cancer registry through the Lymphoid Malignancies Enterprise Architecture Database under an institutional review board–approved protocol. Consent was waived because of the retrospective nature of the project, because individual patients were not interviewed, and because unmasked data were managed in accordance with the Health Insurance Portability and Accountability Act of 1996 privacy standards. Of the 101 patients, 43 had received maintenance therapy after TSEB, 52 had not received maintenance therapy, and the status of 6 patients was unknown.

TSEB Therapy

The patients were treated in a standing position using rotational techniques, including a dual-field technique, using 6-MeV electrons from a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA), as previously described.[11] The cumulative surface dose ranged from 18 to 36 Gy given over 4 to 9 weeks, 3 to 4 days weekly. Eye and nail shields were used. An additional boost was provided to underdosed areas or according to physician preference.

Maintenance

At Emory, maintenance therapy was used at the discretion of the treating physician and included retinoids, PUVA, UVB, extracorporeal photopheresis (ECP), chemotherapy, methotrexate, topical NM, denileukin diftitox, and histone deacetylase inhibitors. Maintenance therapy was defined as therapy that had started either concurrently or within 1 month of TSEB completion, irrespective of the time to progression. Of the 73 patients with progression after TSEB, 16 had developed progression within 1 month of TSEB, including 7 who had received maintenance therapy and 8 who had not.

Response

The response to TSEB was assessed at the end TSEB and included physician examination, laboratory tests, and imaging studies, when indicated. A CR was defined as a $>$ 90% reduction in the cutaneous tumor burden (ie, no visible cutaneous lesions, including the absence of patches, plaques, or diffuse erythroderma).[11] Given the retrospective design and concomitant absence of standardized reassessment tools such as the modified severity weighted assessment tool, CR was determined by the clinical judgment of an adequate response.[19] Progression was defined as worse disease compared with that at the start of TSEB.

Study Design

The primary objective was to assess PFS and OS for patients who had received maintenance therapy after TSEB versus no maintenance therapy. Additional covariates included age at diagnosis, sex, race, diagnosis, International Society of Cutaneous Lymphoma stage, lactate dehydrogenase (LDH), TSEB dose, therapies before and after TSEB, CR to TSEB, and the time to initiating TSEB.

Statistical Analysis

OS was defined as interval from TSEB administration to death or the last follow-up, with those alive at the last follow-up censored. PFS was defined as the interval from TSEB administration to progression, death, or the last follow-up, with the patients without progression at the last follow-up censored. OS and PFS were estimated using the Kaplan-Meier method, and patient characteristics were compared across OS and PFS using log-rank tests. Univariate Cox proportional hazards models were fit for OS and PFS using the patient characteristics specified. In addition, multivariable models were fit for OS and PFS to control for statistically significant covariates found on univariate analysis.

Descriptive statistics were generated for categorical variables using frequencies and percentages and for numeric variables using the mean, median, range, and standard deviation. The categorical patient characteristics were compared across the receipt of maintenance therapy using χ^2 tests or Fisher's exact tests, as appropriate, and numeric variables were compared using analysis of variance (Supplemental Table 1 available in the online version). Statistical

significance was assessed at the $P < .05$ level, and statistical analysis was performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient Characteristics and Treatments

A total of 101 patients with CTCL had received TSEB therapy from 1998 to 2018 at Emory University. The median follow-up was 4.0 years from TSEB administration. The patient characteristics are listed in Table 1. The patients were evenly distributed by sex and race (47% white; 52% black). The most common diagnosis was mycoses fungoides (MF; 66%), followed by Sézary syndrome (16%), CTCL, not otherwise specified (16%), and $CD30^+$ CTCL (1%). The median age at diagnosis was 55 years, consistent with previous reports.[20] Of the 101 patients, 35% had presented at diagnosis with early-stage disease (stage IA-IIA), 65% with advanced-stage disease (stage IIB-IVB), and 49% had an elevated LDH. Some patients had developed progression before TSEB, with a reduction of early-stage disease to 21%.

TSEB was received at a median of 429 days (range, −61 to 4516 days) after the diagnosis. Most patients had received standard-dose therapy instead of low-dose radiation (> 30 Gy, 92%; < 20 Gy, 8%) at 1.5 Gy/fraction (94%). A CR after TSEB was achieved in 79% of maintenance arm and 73% in the no maintenance arm ($P = .63$; Fisher's exact test; Supplemental Table 1 available in the online version). Less than one quarter of patients had exhibited early progression (≤ 4 weeks) after TSEB, with no statistically significant differences between the maintenance and no maintenance groups ($P = .76$; Fisher's exact test).

Of the 101 patients, 45% had received maintenance therapy, most commonly as a single agent (65%) versus combination therapy (35%; Table 1). Retinoids were the most frequently prescribed maintenance regimens (47% of patients), followed by interferon (IFN; 28%), PUVA/UVB (21%), NM (16%), ECP (12%), and other (12%).

We assessed the additional therapies by their temporal association with TSEB (before and after TSEB) and modality (skin-directed, systemic, or local radiotherapy [RT]). Of the 101 patients, 77% had received ≥ 1 therapy before TSEB (median, 2), including 60% skin-directed, 56% systemic, and 14% localized RT. The median number of therapies after TSEB was 2, and 75% of patients had received ≥1 subsequent therapy.

No difference was found in the baseline demographics (sex, race, age), diagnosis, stage, LDH, achievement of CR to TSEB, TSEB dose, treatments before TSEB, or the use of local RT after TSEB between the 2 groups. We did observe a difference in the number of treatments after TSEB (ie, skin, systemic, total), time to TSEB, T stage at TSEB, and interval from TSEB to the next treatment. However, many of these covariates were closely linked to the receipt of maintenance therapy and, thus, were predictably increased in the maintenance group.

Efficacy of Maintenance Therapy Overall

Our primary objective was to evaluate the efficacy of maintenance therapy after TSEB for patients with CTCL. We performed Kaplan-Meier analyses (Figures 1 and 2) and univariate Cox

Table 1 Descriptive Statistics: Patient, Disease, and Treatment Characteristics (n = 101)

Variable	n (%)
Age at diagnosis, y	
Median	55
Range	13-89
Sex	
Male	53 (52.5)
Female	48 (47.5)
Race	
White	46 (46.9)
Black	51 (52.0)
Other	1 (1.0)
Diagnosis	
MF	66 (65.3)
Sézary syndrome	16 (15.8)
$CD30^+$	1 (1.0)
CTCL, NOS	16 (15.8)
Other	2 (2.0)
ISCL stage	
IA-IB	32 (32)
IIA-IIB	36 (36)
IIIA-IIIB	10 (10)
IVA-IVB	22 (22)
LDH	
Normal	28 (50.9)
Elevated	27 (49.1)
Missing	46 (NA)
TSEB dose	
Low (0; <20 Gy)	7 (7.9)
High (>30 Gy)	82 (92.1)
Missing	12 (NA)
Total therapies before TSEB, n	
0	24 (23.8)
1-3	47 (14.9)
>3	30 (8.9)
Complete response after TSEB	
No	22 (23.9)
Yes	70 (76.1)
Missing	9 (NA)
Maintenance therapy	
No	52 (54.7)
Yes	43 (45.3)
Missing	6 (NA)
Maintenance therapy	
RXR	20 (21.1)
PUVA/UVB	9 (9.5)
IFN	12 (12.6)
NM	7 (7.4)
ECP	5 (5.3)
Other	5 (5.3)

Table 1 Continued

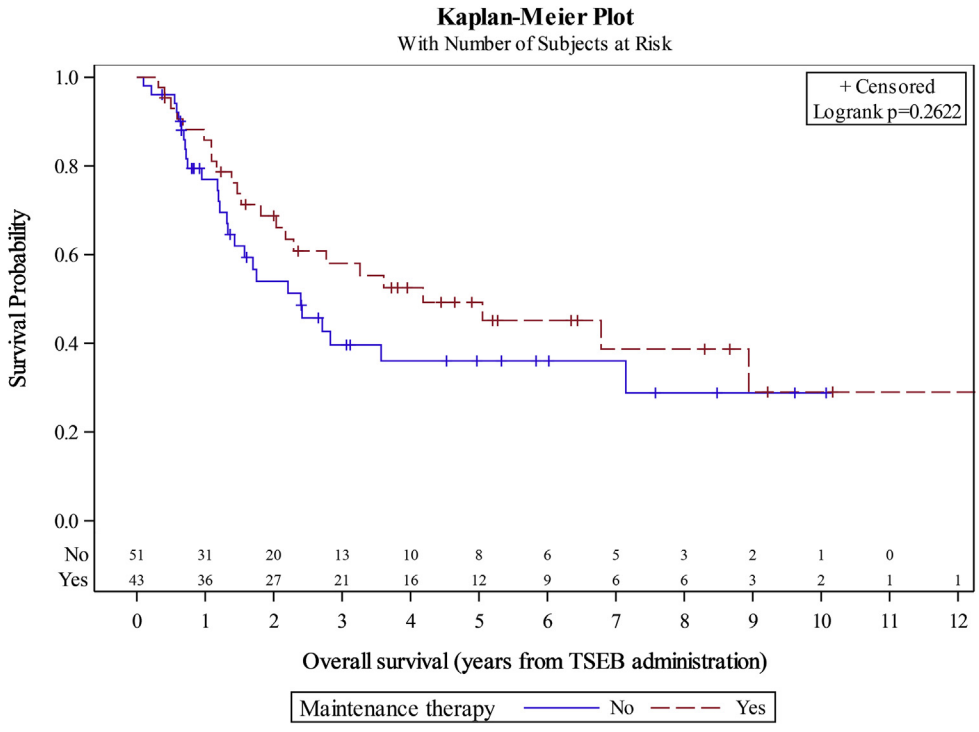
Variable	n (%)
Concurrent maintenance therapy	
Single	28 (65.1)
Combination	15 (34.9)

Abbreviations: CTCL = cutaneous T-cell lymphoma; ECP = extracorporeal photopheresis; IFN = interferon-α; ISCL = International Society of Cutaneous Lymphoma; LDH = lactate dehydrogenase; MF = mycoses fungoides; NA = not applicable; NM = nitrogen mustard; NOS = not otherwise specified; PUVA/UVB = psoralen ultraviolet A or ultraviolet B; RXR = retinoids; TSEB = total skin electron beam therapy.

proportional hazard analyses for OS (Table 2) and PFS, with 29 covariates spanning the demographics, diagnoses, stage, treatments, and initial response. The receipt of any form of maintenance treatment (ie, all maintenance therapies pooled) was associated with a nonsignificant increase in median OS by Kaplan-Meier estimate (4.2 vs 2.4 years; Figure 1) and no difference on univariate analysis (Table 2). In contrast, maintenance therapy was associated with improved PFS on univariate analysis (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.39-0.94; $P = .026$), Kaplan-Meier log-rank test ($P = .025$; Figure 2), and as evidenced by increased 1- and 5-year PFS (1-year PFS, 40.9% vs 25.4%; 5-year PFS, 14.2% vs 4.6%). The following covariates were significantly associated with PFS on univariate analysis: incorporation of maintenance therapy, CR after TSEB, interval to TSEB, and number of local RT sessions before TSEB.

On multivariate analysis for PFS, administration of maintenance therapy (HR, 0.55; 95% CI, 0.34-0.90; $P = .018$) and a CR to TSEB (HR, 0.32; 95% CI, 0.19-0.54; $P < .001$) were significantly associated with increased PFS. In contrast, the receipt of local RT before TSEB (HR, 2.57; 95% CI, 1.37-4.84; $P = .003$) was associated with inferior PFS (Supplemental Table 2 available in the online version).

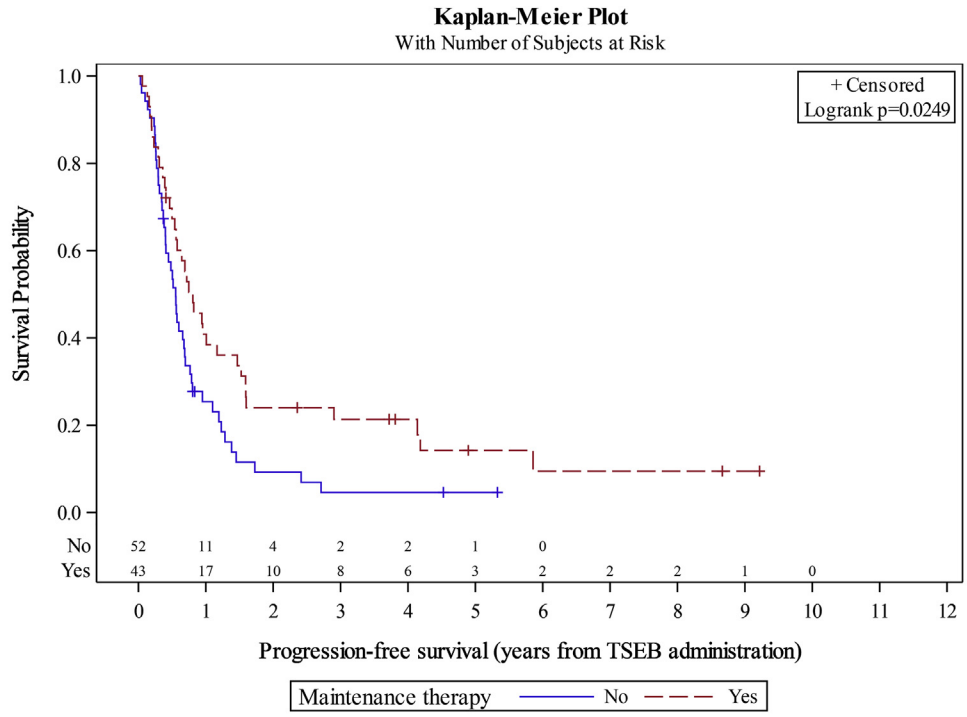
Figure 1 Overall Survival: Maintenance Versus No Maintenance Therapy. Kaplan-Meier Analysis With Log-Rank Test and Median and 1-, 2-, and 5-Year (Yr) Overall Survival Indicated



Maintenance Therapy	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival	5 Yr Survival
No	51	27 (53%)	24 (47%)	2.4 (1.3, 7.1)	77.0% (62.1%, 86.6%)	54.0% (37.8%, 67.7%)	36.0% (21.0%, 51.3%)
Yes	43	23 (53%)	20 (47%)	4.2 (2, NA)	85.8% (71.1%, 93.4%)	68.7% (52.3%, 80.5%)	49.2% (32.6%, 63.9%)

Abbreviations: CI = confidence interval; TSEB = total skin electron beam.

Figure 2 Progression-free Survival: Maintenance Versus No Maintenance Therapy. Kaplan-Meier Analysis With Log-Rank Test and Median and 1-, 2-, and 5-Year (Yr) Progression-free Survival Indicated



Maintenance therapy	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival	5 Yr Survival
No	52	47 (90%)	5 (10%)	0.6 (0.4, 0.7)	25.4% (14.4%, 38.0%)	9.2% (3.0%, 19.8%)	4.6% (0.9%, 13.7%)
Yes	43	36 (84%)	7 (16%)	0.8 (0.5, 1.5)	40.9% (26.1%, 55.1%)	24.0% (12.5%, 37.6%)	14.2% (5.2%, 27.7%)

Abbreviations: CI = confidence interval; TSEB = total skin electron beam.

Efficacy of Individual Maintenance Regimens

We noted significant heterogeneity in the types of maintenance treatments received by our population. To evaluate the effect of the individual maintenance strategies, we performed univariate analyses for OS and PFS for the individual maintenance therapies (retinoids, PUVA/UVB, IFN, NM, ECP, other) versus no maintenance (Table 2, Figure 3). UV therapies (PUVA/UVB), but not other treatments, were associated with improved OS (HR, 0.21; 95% CI, 0.05-0.89; $P = .034$) and PFS (HR for progression, 0.26; 95% CI, 0.11-0.62; $P = .002$) on univariate analysis versus no maintenance. This was confirmed by multivariable Cox models for OS (PUVA/UVB: HR, 0.15; 95% CI, 0.03-0.66; $P = .012$) and PFS (PUVA/UVB: HR, 0.26; 95% CI, 0.11-0.66; $P = .004$; Table 3, Supplemental Table 3 available in the online version).

Nine patients received PUVA/UVB maintenance, including 1 with UVB alone and 8 with PUVA. Of these, 6 had received 1 additional non-PUVA/UVB maintenance therapy in combination (3 with a retinoid, 1 with IFN, 1 with ECP). At diagnosis, of these 9 patients, 3 had had early-stage disease and 6 had had advanced-stage disease, including 1 with B2 stage disease. In terms of possible adverse effects, 1 of the 9 patients receiving PUVA/UVB maintenance subsequently developed nonmelanoma skin cancer.

Factors Associated with OS

In addition to the administration of maintenance UV therapy, as previously described, we identified several favorable patient and treatment characteristics that were associated with increased OS on univariate analysis. These included the diagnosis of MF, high-dose TSEB, a CR after TSEB, an increased number of local RT sessions after TSEB, and an increased number of total therapies after TSEB (Table 2). Additionally, several unfavorable characteristics were associated with reduced OS on univariate analysis: B2 stage,

Table 2 Univariate Analysis of Overall Survival Stratified by Various Patient Characteristics

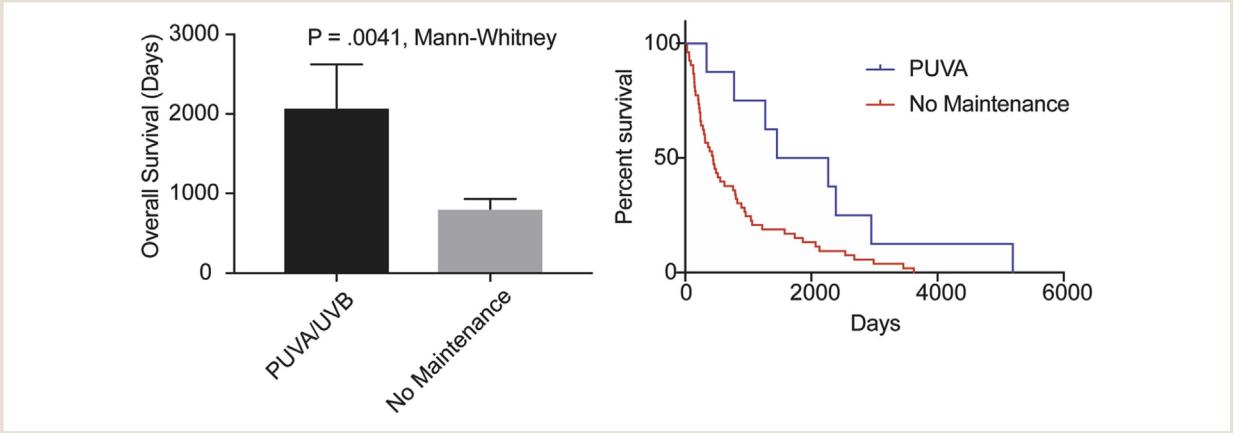
Covariate	Patients, n	OS[a]		
		HR (95% CI)	HR *P* Value	Log-Rank *P* Value
Age at diagnosis	98	1.04 (1.02-1.06)	<.001[b]	NA
Sex				.197
Female	46	0.70 (0.40-1.21)	.199	
Male	52	NA	NA	
Race				.858
Black	50	0.95 (0.55-1.65)	.857	
White, Hispanic, other	45	NA	NA	
Diagnosis				.002[b]
MF	65	0.43 (0.25-0.74)	.002[b]	
Other	33	NA	NA	
T stage at diagnosis				.673
T3	35	1.13 (0.65-1.96)	.673	
Other	59	NA	NA	
B stage at diagnosis				.014[b]
B2	15	2.22 (1.16-4.27)	.017[b]	
Other	80	NA	NA	
T stage at TSEB				.576
T3	43	0.84 (0.46-1.54)	.576	
Other	40	NA	NA	
B stage at TSEB				.180
B2	14	1.64 (0.79-3.39)	.185	
Other	52	NA	NA	
LDH				.038[b]
Elevated	27	2.23 (1.03-4.85)	.043[b]	
Normal	27	NA	NA	
Maintenance therapy				.262
Yes	43	0.73 (0.42-1.27)	.264	
No	51	NA	NA	
Maintenance RXR				.692
Yes	20	1.14 (0.60-2.14)	.693	
No	74	NA	NA	
Maintenance PUVA/UVB				.020[b]
Yes	9	0.22 (0.05-0.89)	.034[b]	
No	85	NA	NA	
Maintenance IFN				.090
Yes	12	0.46 (0.18-1.15)	.098	
No	82	NA	NA	
Maintenance NM				.840
Yes	7	1.13 (0.35-3.65)	.840	
No	87	NA	NA	
Maintenance ECP				.996
Yes	5	1.00 (0.31-3.21)	.996	
No	89	NA	NA	
Other maintenance				.268
Yes	5	1.77 (0.64-4.94)	.275	
No	89	NA	NA	

Table 2 Continued

Covariate	Patients, n	OS[a]		
		HR (95% CI)	HR *P* Value	Log-Rank *P* Value
Combination maintenance				.368
Combination	15	0.66 (0.27-1.63)	.371	
Single	28	NA	NA	
TSEB dose				.028[b]
High (>30 Gy)	81	0.36 (0.14-0.93)	.035[b]	
Low (0; <20 Gy)	6	NA	NA	
Complete response to TSEB				
Yes	69	0.26 (0.14-0.47)	<.001[b]	<.001[b]
No	22	NA	NA	
Time to initiate TSEB (100-d interval; median, 4.23; range, −0.61 to 45.16)	98	0.98 (0.95-1.01)	.289	NA
Time from TSEB to next treatment (100-d interval)	50	0.81 (0.57-1.15)	.240	NA
Skin-directed therapies before TSEB, n				.187
≥1	59	0.69 (0.40-1.20)	.189	
0	39	NA	NA	
Systemic therapies before TSEB, n				.327
≥ 1	56	1.32 (0.76-2.29)	.329	
0	42	NA	NA	
Local RT sessions before TSEB, n				.030[b]
≥1	14	2.12 (1.06-4.24)	.034[b]	
0	84	NA	NA	
Total therapies before TSEB, n				.837
≥4	30	0.90 (0.43-1.89)	.785	
3	20	0.91 (0.41-1.99)	.811	
2	11	0.89 (0.34-2.34)	.807	
1	15	0.56 (0.21-1.49)	.248	
0	22	NA	NA	
Skin-directed therapies after TSEB, n				.028[b]
≥1	33	0.51 (0.28-0.94)	.030[b]	
0	65	NA	NA	
Systemic therapies after TSEB, n				.764
≥1	63	0.92 (0.52-1.62)	.764	
0	35	NA	NA	
Local RT sessions after TSEB, n				.007[b]
≥1	26	0.40 (0.20-0.79)	.009[b]	
0	72	NA	NA	
Total therapies after TSEB, n				.188
≥4	33	0.43 (0.21-0.88)	.021[b]	
3	12	0.65 (0.26-1.60)	.351	
2	14	0.67 (0.27-1.67)	.394	
1	14	0.87 (0.35-2.17)	.773	
0	25	NA	NA	

Abbreviations: CI = confidence interval; ECP = extracorporeal photopheresis; HR = hazard ratio; IFN = interferon-α; LDH = lactate dehydrogenase; MF = mycoses fungoides; NA = not applicable; NM = nitrogen mustard; PUVA/UVB = psoralen ultraviolet A or ultraviolet B; RT = radiotherapy; RXR = retinoids; TSEB = total skin electron beam therapy.
[a]OS defined as years after TSEB administration.
[b]Statistically significant.

Figure 3 Overall Survival With Psoralen and Ultraviolet A (PUVA) Versus No Maintenance Treatment



Abbreviation: UVB = ultraviolet B.

elevated LDH, an increased number of local RT sessions before TSEB, and advanced age (Table 2). We performed multivariable analysis to further assess these factors (Supplemental Table 4 available in the online version). Of the 10 significant covariates found on univariate analysis, we omitted the number of treatments after TSEB, because this likely reflected a survival bias. We also excluded high-dose TSEB, which has been studied extensively elsewhere and accounted for most (92%) of the patients in our cohort.[5] We also omitted a diagnosis of MF because non-MF disease, including Sézary syndrome, was redundant, being largely captured by B2 stage. Several missing values were found in our database for the baseline LDH, which has been previously studied[20]; therefore, the LDH level also excluded. We included the remaining 4 covariates (CR after TSEB, B2 stage, increased number of local RT sessions before TSEB, and advanced age) in a multivariable Cox model and confirmed that all 4 were independent predictors of OS: CR (HR, 0.33; 95% CI, 0.18-0.61; $P < .001$), B stage at diagnosis (HR, 2.08; 95% CI, 1.04-4.14; $P = .037$), administration of local RT before TSEB (HR, 2.44; 95% CI, 1.16-5.14; $P = .019$), and age at diagnosis (HR, 1.05; 95% CI, 1.02-1.08; $P < .001$).

Table 3 Multivariable Analysis of Overall Survival for PUVA/UVB

Covariate	HR (95% CI) for OS	HR *P* Value for OS
PUVA/UVB maintenance		
Yes	0.15 (0.03-0.66)	.012[a]
No	0.88 (0.48-1.60)	.671
No maintenance	NA	NA
B stage at diagnosis (B2 vs. other)	1.83 (0.91-3.66)	.089
Complete response (yes vs. no)	0.26 (0.14-0.50)	<.001[a]
Age at diagnosis	1.05 (1.03-1.08)	<.001[a]

A multivariable Cox proportional hazard model was fit for OS with the significant variables from the univariate analyses: PUVA/UVB, B stage at diagnosis, complete response, age at diagnosis; the number of observations in the original data set was 101; number of observations used was 89.
Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; PUVA/UVB = psoralen ultraviolet A or ultraviolet B; TSEB = total skin electron beam therapy.
[a]Statistically significant.

Discussion

We conducted a single-center retrospective analysis of 101 patients with all stages of CTCL to evaluate the outcomes with maintenance therapy after TSEB. In our institution, maintenance therapy was associated with improved PFS on both univariate and multivariate analysis, with a 1-year PFS rate of 25% without versus 41% with maintenance therapy. Numerically, survival was nearly double for the patients who received maintenance therapy compare with those who had not received maintenance therapy (median OS, 4.2 vs. 2.4 years). However, the difference did not reach statistical significance owing to the limited sample size ($P = .26$).

Our exploratory analysis of the individual maintenance regimens further demonstrated an effect on OS with UV-based maintenance, which was confirmed on multivariate analysis (Figure 3). Several patients who had received PUVA/UVB had had high-risk features, including advanced-stage disease with blood (B2) stage. However, these findings will need to be confirmed in larger randomized prospective studies.

We also confirmed the prognostic value of several factors in our cohort and identified some novel associations. In our population, local RT before TSEB was associated with inferior OS and PFS. B2 stage at diagnosis and advanced age were also predictors of poor outcomes. Similar to previous studies, the achievement of a CR after TSEB was associated with improved OS and PFS. The significance of previous local RT before TSEB also requires further exploration.[5,20-26]

TSEB is a highly effective therapy for CTCL; however, the duration of the response has often been limited, especially for patients with advanced-stage disease. Maintenance therapy after TSEB has been assessed in a number of previous studies; however, these studies were largely from the late 1990s to early 2000s, had small patient numbers, and had reported mixed outcomes.[13-18,27-30] Although a variety of skin-directed and systemic therapies have

Table 4 Selected Previous Studies Assessing Maintenance Therapy

Investigator	Study Design	Stage	Patients, n	Treatment (n)	CR (%)	OS (%)	PFS/DFS (%)	Other
Jones et al,[27] 1992	Prospective vs. retrospective (control)	T1-T2	23	TSEB alone; TSEB + etretinate	NR	NR	Similar DFS in both arms	NR
Wilson et al,[17] 1995	Retrospective	All	163	T1-T2: TSEB alone; TSEB + chemotherapy; TSEB + ECP; T3-T4: TSEB alone; TSEB + chemotherapy; TSEB + ECP	NR	T1-T2: 70% (3-5 y); 95% (3-5 y); 100% (3-5 y; $P < .03$); T3-T4: 30% (5 y); 70% (5 y); 75% (5 y; $P < .05$)	No difference for T1-T2 or T3-T4	NR
Quiros et al,[14] 1997	Retrospective	T1-T2	114	TSEB + PUVA; TSEB + other[a]	NR	100 (5 y); 82 (5 y; $P < .1$, NS)	85 (5 y); 50 (5 y; $P < .02$)	Improved DFS but not OS
Chinn et al,[16] 1999	Retrospective	T2	55	TSEB alone; TSEB + NM	66; 100	14.2 y; 7.8 y (median)	TSEB + NM vs. TSEB alone ($P = .068$)	No difference in CSS or OS; trend for improved FFR with maintenance
Wilson et al,[17] 2000	Retrospective	T4	44	TSEB alone; TSEB + ECP	71; 74	63 (2 y); 88 (2 y; $P = .14$)	49 (2 y); 93 (2 y; $P = .024$)	CSS: 69 (2 y); 100 (2 y; $P = .048$)
Duvic et al,[28] 2003	Retrospective cohort	All	95	IFN + oral RXR, then TSEB, then NM + PUVA	76; 41 ($P < .01$)	94 (5 y); 35 (5 y; $P < .0001$)	50 (5 y); 27 (5 y; $P = .03$)	NR
Roberge et al,[13] 2007	Retrospective	All	50	TSEB alone; TSEB + IFN	65; 58 ($P = .4$)	61 mo; 38 mo (median; $P = .4$)	95.5 mo; 7.4 mo (median; $P = .003$)	NR
Sanchez et al,[29] 2011	Prospective cohort	IA-IB	40	PUVA alone; PUVA + PUVA maintenance	NR	NR	NR	No difference in risk of relapse by PUVA maintenance
Wagner et al,[15] 2013	Retrospective	All	41	TSEB alone; TSEB + IFN concurrent	36; 63 ($P = .15$)	58 (5 y) for all patients (HR, 1.27; $P = .65$); no difference by group	33 (5 y) for all patients (HR, 1.2; $P = .66$); no difference by group	No difference in OS or PFS
Bagot et al,[30] 2017	Phase III randomized trial	AS	21	Chemotherapy[b] alone; chemotherapy[b] + lenalidomide	NR	NR	2 mo (median); 5.3 mo (median); $P = NS$	Study halted for rapid progression in 4 wk in 1/3 of patients with no maintenance

Abbreviations: AS = advanced stage; CR = complete response; CSS = cancer-specific survival; DFS = disease-free survival; ECP = extracorporeal photopheresis; FFR = freedom from relapse; IFN = interferon-α; NM = nitrogen mustard; OS = overall survival; PFS = progression-free survival; PUVA/UVB = psoralen ultraviolet A or ultraviolet B; RXR = retinoid; TSEB = total skin electron beam therapy.
[a]Mostly chemotherapy.
[b]One patient also received TSEB.

been proposed as maintenance options after TSEB, the single randomized trial to test the efficacy of maintenance therapy was halted early because of poor accrual.[13-18,27-30] Our study compares favorably and supports previous findings regarding maintenance therapy for this disease. The strongest data in support of maintenance therapy for early-stage CTCL derive from 2 retrospective analyses from the late 1990s. An analysis of NM maintenance after TSEB in patients with stage T2 disease demonstrated a longer freedom from relapse in the TSEB plus NM group compared with TSEB alone ($P = .068$).[16] However, no OS difference was detected.[16] Similarly, adjuvant PUVA as a maintenance strategy was assessed in 114 patients with limited (stage T1-T2) skin disease after TSEB to a dose of 36 Gy.[14] The 5-year DFS was 85% versus 50% in favor of PUVA, and survival, although the difference was not statistically significant, was numerically greater in the PUVA maintenance arm (100% vs 82% at 5 years).[14] Two additional retrospective analyses had studied differing methods of adjuvant therapy for advanced-stage disease. In patients with advanced disease (stage T3-T4) who had had a CR to TSEB, the addition of ECP after TSEB appeared to be beneficial, with a 5-year OS of 100% compared with only 50% for patients not receiving maintenance ($P < .06$).[17] A closer examination of ECP for patients with stage T4 disease also showed improvements in 2-year PFS (36% vs 66%; multivariate $P = .074$) and cancer-specific survival with maintenance therapy (multivariate $P = .048$).[18] However, more recent analyses have failed to demonstrate a benefit with maintenance therapy after TSEB, which might have partially resulted from inadequately powered studies (Table 4).[15,29,30] Overall, 4 of 10 studies evaluating maintenance concurrently or after TSEB had found an effect for DFS and PFS (maintenance improved DFS and PFS in 3 studies and had worsened PFS and DFS in 1 study), and 1 study found a positive effect for maintenance on cancer-specific survival. Collectively, these studies identified benefit with NM, PUVA, and ECP but not with IFN, retinoids, or chemotherapy. In our study and previous studies, UV-based therapies were unique in their apparent ability to prolong survival after TSEB. Although multiple mechanisms of action have been proposed for UV treatment, both RT and UV therapy result in DNA damage. We speculate that this mechanism of action might be critical to the improved survival in our patients by targeting the unstable CTCL genome (65% of CTCL cases will exhibit chromothripsis compared with 5% of other cancer cases, presumably from RAG [recombination-activating gene]-mediated recombination).[31]

Our study had several strengths, including our relatively large cohort of patients with CTCL who had received TSEB, detailed clinical annotation of the patients, near uniformity in TSEB treatment, and the inclusion of modern RT techniques such as rotational TSEB. Our study also had some limitations, including those inherent to retrospective studies. Our population was heterogeneous by stage and line of therapy, with numerous maintenance therapies and combinations, which limited our ability to evaluate the efficacy of individual agents in a select cohort. Nonetheless, we applied univariate and multivariable analyses to evaluate the efficacy of maintenance therapy on OS and PFS in our diverse cohort. We analyzed all patients with CTCL who had received TSEB. However, with more statistical power, further subdivision of the patients to select for high-risk cohorts, such as those who had received systemic therapy (instead of skin-directed therapy), those with progression before TSEB, and/or those who had undergone allogeneic hematopoietic stem cell transplantation, could yield additional insights. Given the clinical benefit observed in our study, it is worth noting that TSEB is mainly available at academic centers and CTCL centers and not universally.

Conclusion

We found that all-comer maintenance therapy after TSEB was associated with prolonged PFS and that the specific maintenance regimen of UV therapy was associated with improved OS. Our data support the additional study of maintenance therapy, in particular, UV maintenance, after TSEB in larger analyses.

Clinical Practice Points

- In previous studies, maintenance therapy after TSEB had demonstrated mixed results for PFS, with no significant effects on OS.
- In our study, maintenance therapy improved PFS for patients with all stages of CTCL.
- In our study, UV-based maintenance improved PFS and OS in a subset of patients with CTCL.
- Our data support the use of maintenance therapy, especially UV therapy, for patients with CTCL.
- More multicenter and prospective studies are needed to fully evaluate UV-based maintenance therapies after TSEB for CTCL.

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Disclosure

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Supplemental Data

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Supplemental Data

Supplemental Table 1 Treatment Comparisons

Covariate	Maintenance		*P* Value[a]
	No (n = 52)	Yes (n = 43)	
Sex			.328
Male	25 (48.08)	25 (58.14)	
Female	27 (51.92)	18 (41.86)	
Race			.320
White, Hispanic, other	21 (42)	22 (52.38)	
Black	29 (58)	20 (47.62)	
Diagnosis			.852
Other	16 (30.77)	14 (32.56)	
MF	36 (69.23)	29 (67.44)	
T stage at diagnosis			.059
Other	34 (69.39)	21 (50)	
T3	15 (30.61)	21 (50)	
B stage at diagnosis			.243
Other	44 (88)	34 (79.07)	
B2	6 (12)	9 (20.93)	
T stage at TSEB			.018[b]
Other	25 (59.52)	13 (33.33)	
T3	17 (40.48)	26 (66.67)	
B stage at TSEB			.424
Other	28 (82.35)	23 (74.19)	
B2	6 (17.65)	8 (25.81)	
LDH			.273
Normal	17 (56.67)	10 (41.67)	
Elevated	13 (43.33)	14 (58.33)	
TSEB dose			1.000
Low (0; <20 Gy)	3 (6.67)	2 (4.76)	
High (>30 Gy)	42 (93.33)	40 (95.24)	
Skin therapies before TSEB, n			.341
0	18 (34.62)	19 (44.19)	
≥1	34 (65.38)	24 (55.81)	
Systemic therapies before TSEB, n			.572
0	20 (38.46)	19 (44.19)	
≥1	32 (61.54)	24 (55.81)	
Local therapies before TSEB, n			.437
0	43 (82.69)	38 (88.37)	
≥1	9 (17.31)	5 (11.63)	
Total therapies before TSEB, n			.749
0	10 (19.23)	10 (23.26)	
1	7 (13.46)	8 (18.6)	
2	5 (9.62)	6 (13.95)	
3	11 (21.15)	8 (18.6)	
≥4	19 (36.54)	11 (25.58)	
Skin therapies after TSEB, n			<.001[b]
0	42 (80.77)	20 (46.51)	
≥1	10 (19.23)	23 (53.49)	
Systemic therapies after TSEB, n			.006[b]
0	25 (48.08)	9 (20.93)	
≥1	27 (51.92)	34 (79.07)	
Local therapies after TSEB			.209
0	41 (78.85)	29 (67.44)	
≥1	11 (21.15)	14 (32.56)	
Total therapies after TSEB, n			.008[b]
0	21 (40.38)	4 (9.3)	
1	8 (15.38)	5 (11.63)	
2	6 (11.54)	7 (16.28)	
3	4 (7.69)	7 (16.28)	
≥4	13 (25)	20 (46.51)	
Complete response			.530
No	13 (26.53)	9 (20.93)	
Yes	36 (73.47)	34 (79.07)	
Age at diagnosis, y			.720
Patients, n	52	43	
Mean	54.88	53.81	
Median	58	55	
Time to initiate TSEB (100-d interval)			.050[b]
Patients, n	52	43	
Mean	10.1	6.04	
Median	4.52	3.41	
Time from TSEB to next treatment (100-d interval)			<.001[b]
Patients, n	21	28	
Mean	0.83	−0.05	
Median	0.65	−0.01	

Data presented as n (column %), unless noted otherwise.
Abbreviations: LDH = lactate dehydrogenase; MF = mycoses fungoides; TSEB = total skin electron beam (therapy).
[a]*P* value calculated using analysis of variance for numerical covariates and the χ^2 test or Fisher's exact for categorical covariates, as appropriate.
[b]Statistically significant.

Supplemental Table 2 Multivariable Analysis of PFS

Covariate	HR (95% CI) for PFS	HR *P* Value for PFS
Maintenance therapy (yes vs. no)	0.55 (0.34-0.90)	.018[a]
Time to initiate TSEB (100-d interval)	0.98 (0.95-1.00)	.052
No. of local therapies before TSEB (≥ 1 vs. 0)	2.57 (1.37-4.84)	.003[a]
Complete response (yes vs. no)	0.32 (0.19-0.54)	<.001[a]

Number of observations in the original data set was 101; number of observations used was 92.
Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; TSEB = total skin electron beam therapy.
[a]Statistically significant.

Supplemental Table 3 Multivariable Analysis of PFS for PUVA

Covariate	HR (95% CI) for PFS	HR *P* Value for PFS
PUVA/UVB		
Yes	0.26 (0.11-0.66)	.004[a]
No	0.91 (0.56-1.47)	.697
No maintenance	NA	NA
B stage at diagnosis (B2 vs. other)	1.09 (0.60-1.97)	.778
No. of local therapies before TSEB (≥ 1 vs. 0)	2.75 (1.47-5.17)	.002[a]
Complete response (yes vs. no)	0.31 (0.18-0.53)	<.001[a]

Number of observations in the original data set was 101; number of observations used was 90.
Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; PFS = progression-free survival; PUVA = psoralen ultraviolet A; TSEB = total skin electron beam therapy; UVB = ultraviolet B.
[a]Statistically significant.

Supplemental Table 4 Multivariable Analysis of OS

Covariate	HR (95% CI) for OS[a]	HR *P* Value for OS[a]
Complete response (yes vs. no)	0.33 (0.18-0.61)	<.001[b]
B stage at diagnosis (B2 vs. other)	2.08 (1.04-4.14)	.037[b]
No. of local therapies before TSEB (≥ 1 vs. 0)	2.44 (1.16-5.14)	.019[b]
Age at diagnosis	1.05 (1.02-1.08)	<.001[b]

Number of observations in the original data set was 101; number of observations used was89.
Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; TSEB = total skin electron beam therapy.
[a]OS defined as years from TSEB.
[b]Statistically significant.