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Total skin electron beam therapy for primary cutaneous T-cell lymphomas: clinical characteristics and outcomes in a Mexican reference center☆

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ABSTRACT

Aim: The aim of this study was to assess treatment modalities, treatment response, toxicity profile, disease progression and outcomes in 14 patients with a confirmed diagnosis of primary cutaneous T-cell lymphoma (PCTCL) treated with total skin electron beam therapy (TSEBT).
Background: Primary cutaneous lymphomas (PCLs) are extranodal non-Hodgkin lymphomas originating in the skin without evidence of extracutaneous disease at diagnosis. Despite advances in systemic and local therapy options, the management of advanced stages remains mostly palliative.
Materials and Methods: This is a retrospective study of patients with PCTCL, diagnosed and treated in a reference center in Mexico City, analyzing treatment modalities, response to treatment, long-term outcome, and mortality.
Results: Eight males (57%) and 6 (43%) females were identified. Most patients were stage IVA (n = 5, 36%) followed by stage IB and IIB (28.5% and 21.4%, respectively). Eleven patients received the low-dose RT scheme (12 Gy), 1 patient, the intermediate-dose RT scheme (24 Gy), and 2 patients, the conventional-dose RT scheme (36 Gy). Mean follow-up time was 4.6 years. At first follow-up examination, 6–8 weeks after radiotherapy, the overall response rate (ORR) for the cohort was 85%. The median PFS for the whole cohort was 6 months.
Conclusion: This study reinforces the role of TSEBT when compared with other treatment modalities and novel agents. Low-dose TSEBT is now widely used because of the opportunity for retreatment.

1. Background

Primary cutaneous lymphomas (PCLs) are extranodal non-Hodgkin lymphomas (NHLs) that originated in the skin without evidence of extracutaneous disease at diagnosis. Cutaneous T-cell lymphomas represent 13% of all NHLs.[1] The incidence of primary cutaneous T-cell lymphomas (PCTCLs) is 10.2 per million persons.[2] For a lymphoma to be categorized as primary cutaneous, the lymphocytic proliferation has to be limited to the skin with no involvement of the lymph nodes, blood, bone marrow, or viscera at diagnosis. Despite advances in systemic and local therapy options, the management of advanced stages remains mostly palliative, as PCTCL is known to be an incurable disease.[3] Mycosis Fungoides (MF) is the most common malignancy and accounts for 60% of PCTCLs and almost 50% of all PCLs[4]; Sézary syndrome (SS) is the second most common.

Treatment of PCTCLs is stage-based, with skin-directed therapies (e.g., ultraviolet [UV] light, topical corticosteroids, nitrogen mustard and/or retinoids) constituting the main strategies for treating early-stage MF and systemic therapies (e.g., retinoids, chemotherapy, and targeted therapy) constituting the main strategy to treat advanced disease (i.e., those with extensive plaque and advanced tumor stage).[5] In patients with extensive skin

Abbreviations: CI, Confidence interval; CR, Complete response; EORTC, European Organisation for Research and Treatment of Cancer; LCT, Large cell transformation; LPD, Lymphoproliferative disorder; MF, Mycosis fungoides; NHL, Non-Hodgkin lymphomas; ORR, Overall response rate; OS, Overall survival; PCL, Primary cutaneous lymphoma; PCTCL, Primary cutaneous T-cell lymphomas; PFS, Progression-free survival; RT, Radiotherapy; SD, Standard deviation; SS, Sézary syndrome; TSEBT, Total skin electron beam therapy; UV, Ultraviolet.

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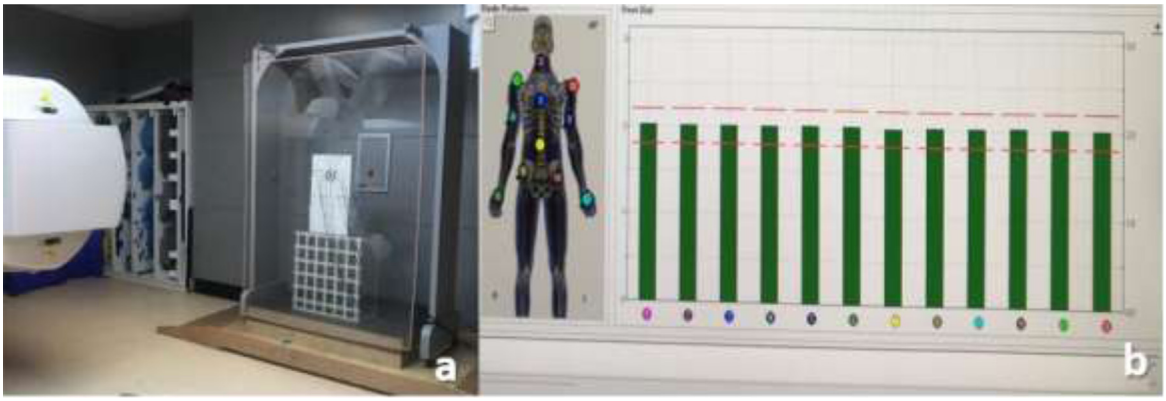

Fig. 1. a. Dosimetry test performed using a plane-parallel ion chamber, twelve semiconductor diodes, an in-vivo dosimetry electrometer. Fig. 1.**b.** Vivo Soft software showing lectures captured by semiconductor diodes.

involvement and refractory disease, total skin electron beam therapy (TSEBT) is an important option for management and uses radiation doses from 12 Gy to 36 Gy. Formerly, the TSEBT radiation doses ranged from 30 Gy to 36 Gy. However, recurrences invariably occur even with high radiation doses, so TSEBT with lower radiation doses has become popular due to comparable rates of remission (reaching 95%) with shorter treatment periods, fewer side effects, and the opportunity of retreatment.[6]

1.1. Aim

The aim of this study was to assess treatment modalities, treatment response, toxicity profile, disease progression, and outcomes in 14 patients with a confirmed diagnosis of PCTCL treated with TSEBT in a reference center.

2. Materials and methods

2.1. Patient characteristics

We conducted a retrospective study of patients with a diagnosis of PCTCL evaluated at our institution from September 2015 to September 2019. The study protocol was approved by the institutional review board. Patients signed informed consent for TSEBT, data analysis and serial photographs for monitoring response to radiotherapy. A comprehensive database of patients who received radiotherapy was used to identify patients with a diagnosis of PCTCL. Patients' electronic and paper-based medical records were reviewed. In all patients, the diagnosis and staging were made according to the World Health Organization European Organization for Research and Treatment of Cancer (EORTC) classification.[7] A total of 14 patients with both clinical and histologic diagnoses of PCTCL were included.

2.2. Clinical and histopathological data

Data collected for this study consisted of patient age at diagnosis, gender, stage at diagnosis, stage progression, large cell transformation (LCT), pruritus, alopecia, body region of skin involvement, morphology of lesions, treatment modalities, response to treatment, long-term outcome, and mortality. Treatment modalities were collected for every patient.

2.3. Implementation of TSEBT and dosimetry aspects

Before the implementation of TSEBT in our institution, a strong dosimetry evaluation was made. Support by our biomedical engineering department was needed for fabricating an acrylic beam spoiler of 1.8 m height, 1.3 m width and 0.5 mm thick. A 6 MeV electron beam of a Truebeam linear accelerator V2.5 (Varian Medical Systems, Palo Alto, CA) was used as the radiation source. To characterize the high electron beam dose rate, percentage depth dose (PDD) for the 6 MeV energy at distances of 1 m and 3.5 m from the surface of the phantom (water-equivalent RW3 slab phantom, model T29672, PTW, Freiburg, Germany) in a field of 36×36 cm using a plane-parallel ion chamber (Advanced Markus Model N34045, PTW, Freiburg, Germany) were performed. The measurements were made at 3.5 m with the acrylic screen located 3.3 m from the beam exit and 20 cm from the irradiated surface to obtain a dose rate of 2500 UM/min. For obtaining correction coefficients (CC) twelve semiconductor diodes were placed on the surface of a solid water phantom and a plane-parallel ion chamber to a maximum depth of 1 cm for the 6 MeV electron beam, with a cone field of a 20×20 cm and a distance of 3.5 m from the isocenter. The absorbed dose was determined by the input diode and ionization chamber with the gantry set at 270° degrees as shown in Figs. 1**.a. and 1.b.** The CC were given by the following equation:

$$CC = Readingoftheionizationchamber/Readingofthediode$$

TSEBT was implemented at our institution in 2015. Since then, we have performed in vivo dosimetry for every patient at day one and two of the radiation regimen. The 6-dual field technique better known as Stanford Technique is used, which includes the patient standing in anterior, posterior, and four opposed oblique positions **(**Figs. 2**a and 2b)**. Radiation is delivered using dual gantry angles of 282.5 y 257.5 degrees. Three fields are treated each day, four days per week, consisting usually of the anterior field with two posterior oblique fields on day one followed by the posterior with two anterior oblique fields on the second day as described by Hoppe et al.[8,9] Twelve semiconductor diodes are set in head and neck, thorax, left and right hip, both arms, hands, legs and at the isocenter. An in-vivo dosimetry electrometer (VIVODOS T10018, PTW, Freiburg, Germany) and VivoSoft software are used to register the readings obtained by the diodes when radiation is administered in each of the six fields. Monitor Units (MU) were corrected by a mean value of 137 MU (±104, range 12–302). Schüttrumpf et al. have discussed dose optimization of TSEBT with thermoluminescent dosimetry for adjustment of the MU to obtain an accurate prescription dose.[10] Personalized shielding is used for the eyes, scrotum and nails if not involved **(**Fig. 3**)**. A total skin dose of 2 Gy is delivered over each 2-day cycle including the soles of the feet. When underdosed areas are measured by semiconductor diodes, such as self-shielding areas like the top of the scalp and perineum, additional 10–12 Gy boost fields with 6–9 MeV are given to achieve planned dose prescription

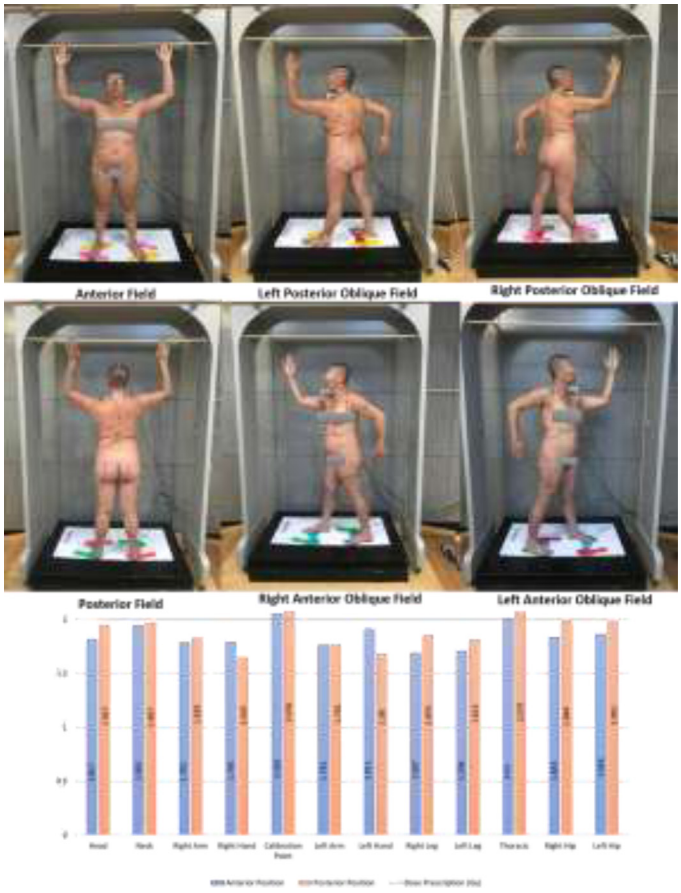

Fig. 2. a. In-vivo dosimetry of a patient with PCTCL to adjust MU in underdosed areas. The anterior field with two posterior oblique fields on day one followed by the posterior with two anterior oblique fields on the second day were administered. Fig. 2**.b.** Vivo soft reading of in-vivo dosimetry. Abbreviations: PCTCL, primary cutaneous T-cell lymphoma.

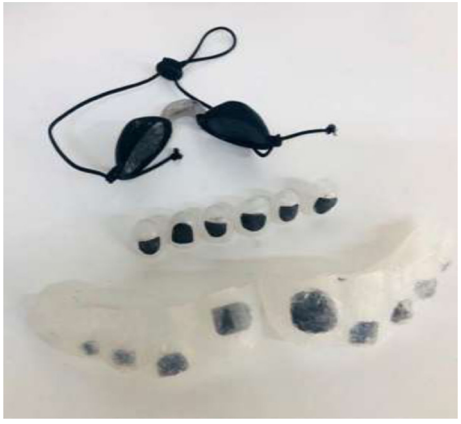

Fig. 3. Personalized shielding of eyes and nails is made for every patient treated at our Institution.

depending on the body region and the absorbed dose in it. When residual disease is suspected we offer 12 Gy additional boosts.

2.4. Clinical endpoints and response criteria

The clinical endpoints and response criteria used in this study were adapted from consensus criteria by the International Society for Cutaneous Lymphomas, EORTC, and the United States Cutaneous Lymphoma Consortium.[11] A complete response was defined as having no skin lesions at the time of the last clinical assessment. Partial response was defined as >50% clearance of skin lesions from baseline. No response to TSEBT was documented when patients' skin lesions did not improve (<50% improvement) or when the skin condition worsened at the next follow-up exam. The duration of response was defined as the time of documentation of skin response to therapy, disease progression/relapse, or when patients were lost to follow-up.

2.5. Statistical analysis

Descriptive statistics were used to report demographic data, therapy modalities, and response rates. Continuous data are expressed as mean ± standard deviation (SD) or median (range), as appropriate. The non-parametric Kruskal-Wallis H test was employed to determine if there were statistically significant differences between the three groups of an independent variable (radiotherapy [RT] scheme) on the ordinal dependent variables. A P-value of <0.05 was considered statistically significant.

The Kaplan-Meier and Log Rank methods were used to analyze survival rates. Overall survival (OS) was obtained from the date of diagnosis to the date of death from any cause or last date of known follow-up. For calculation of progression-free survival, the date of first disease recurrence or disease-related death were considered as events. All analyses were performed using STATA Version 15 (StataCorp LLC, College Station, TX).

3. Results

The demographic data of 14 patients are summarized in Table 1. Eight male (57%) and 6 (43%) female patients treated with TSEBT were identified. The male-to-female ratio was 1.3:1. Two patients had MF, 5 had SS, and 7 had non-MF/SS PCTCLs. The median age at diagnosis was 63 years (range, 17–74) years. Disease staging was documented and analyzed at diagnosis and at disease progression. At diagnosis, most patients were stage IVA (n = 5; 36%) followed by stage IB and IIB (28.5% and 21.4%, respectively). LCT was documented in 1 (7.14%) patient, in whom stage IIB was the initial stage at diagnosis. Patients were treated with 12 Gy, 24 Gy or 36 Gy according to the severity of the disease and were grouped as follows: 11 patients received the low-dose RT scheme (12 Gy), 1 patient the intermediate-dose RT scheme (24 Gy), and 2 patients, the conventional-dose RT scheme (36 Gy). Mean follow-up time was 4.6 years (median, 2 years; range, 0–18 years). Boost or supplemental radiation (range, 10–12 Gy) was delivered to 7/14 patients (50%) to compensate for underdosing in shadowed body areas (e.g., medial thigh, plantar surfaces perineum, and scalp) or for treatment of residual lesions. One patient received concurrent subcutaneous interferon during TSEBT with 12 Gy.

3.1. Clinical presentation and histopathology

The predominant clinical presentations included plaques in 7 patients (50%) followed by patches in 2 (14%), follicular papules in 1 (7%), and tumors in 1 patient (Figs. 1a, 1b). Thirteen patients (93%) suffered from pruritus. The lower and upper extremities were the main sites of involvement in 6 patients (43%). Other frequently affected areas included the head/face (14%) and chest (28.5%). The clinicopathological categorization of PCTCLs is summarized in Table 1.

3.2. Treatment response

The most commonly used treatments before radiation therapy were phototherapy in 9 patients, oral methotrexate in 7, and topical

Table 1
Characteristics of the Whole Cohort.

Demographics	n (%)
	14 (100)
Median Age (SD)	63 (17.3)
Gender	
Female	6 (42.86)
Male	8 (57.14)
Stage at Diagnosis	
IA	1 (7.14)
IB	4 (28.57)
IIA	0 (0)
IIB	3(21.43)
IIIA	0 (0)
IIIB	0 (0)
IVA1	3 (21.43)
IVA2	2 (14.29)
IVB	1 (7.14)
Large Cell Transformation	
Yes	1 (7.14)
No	13 (92.86)
Histopathology	
Mycosis Fungoides	2 (14.29)
Sézary Syndrome	5 (35.71)
Primary cutaneous CD4+	1 (7.14)
small/medium T-cell	3 (21.43)
lymphoproliferative disorder	3 (21.43)
Primary cutaneous peripheral	
T-cell lymphoma, NOS	
Primary cutaneous CD30+	
Lymphoproliferative Disorders	
Clinical Presentation	
Tumor	1 (7.14)
Erythroderma	3 (21.43)
Papulo-nodules	1(7.14)
Plaques	7 (50.0)
Patches	2 (14.29)
Pruritus	13 (92.8)
Predominant Body Area of Skin	
Involvement	3 (21.43)
Generalized	4 (28.57)
Head and Neck	4 (28.57)
Trunk	1 (7.14)
Abdomen	2 (14.29)
Extremities	
Survival Status	
Alive	9 (64.29)
Death	5 (35.71)

Table 2
Treatment offered before TSEBT and after recurrence of disease.

Characteristics	n (%)
Previous Treatments[a]	
Cyclophosphamide	3 (21.42)
Methotrexate	7 (50.00)
Phototherapy (UVA/UVB)	9 (64.28)
Thalidomide	1(7.14)
CHOP Chemotherapy Regimen	3 (21.42)
Brentuximab	1 (7.14)
Interferon	3 (21.42)
Adriamycin	2(14.28)
Gemcitabine	1 (7.14)
Topical Retinoids	1 (7.14)
Topical Corticosteroids	7 (50.0)
Oral Corticosteroids	4 (28.57)
Topical Tacrolimus	1 (7.14)
Fludarabine	1 (7.14)
Vorinostat	1(7.14)
Bortezomib	1 (7.14)
Vincristine	1 (7.14)
Cytarabine	1 (7.14)
Treatment for Recurrence after	
TSEBT[a]	1 (7.14)
CHOP Chemotherapy Regimen	1 (7.14)
Brentuximab	1 (7.14)
Phototherapy	4 (28.57)
Topical Corticosteroids	1 (7.14)
Topical Imiquimod	1 (7.14)
Topical Tacrolimus	

[a] Used alone or in combination. Abbreviations: NOS, no other specified; TSEBT, total skin electron beam therapy; UV, ultraviolet.

corticosteroids in 7 followed by diverse chemotherapy agents (see Table 2).

The median number of treatments used per patient was 3 (range, 1–11), either given subsequently or as combination treatments. A small number of myeloablative and nonmyeloablative allogeneic and autologous stem cell transplantations for these patients have been reported in literature[12,13]; however, none of our patients was offered this treatment modality. TSEBT was given to those patients who were refractory to multiple skin directed therapies (See Figs. 4a and 4b). TSEBT radiation was initiated in 14 patients. At the first follow-up examination 6–8 weeks after radiotherapy, overall response rate (ORR) was achieved in 12 patients (85.7%) with complete response (CR) in 6 patients and partial response in 6 patients. For MF patients CR was obtained in 50%, for SS patients PR was achieved in 60% with no patient achieving CR, for non-MF/SS PCTCLs patients CR was obtained in 71.4% ($p = 0.486$). The median dose for TSEBT was 12 Gy (range, 12–36; Table 3). The nine patients alive are currently under PUVA maintenance therapy.

3.3. Disease progression and survival rates

The mean duration of follow-up from diagnosis was 4.6 years (median, 2 years; range, 0–18 years). The median duration of follow up period from TSEBT was 10 months (range, 6 days to 3 years). The median progression-free survival (PFS) for the whole cohort was 6 months (range, 3–25 months); the PFS rates after 2 years in patients with MF was 100%. In SS patients, the PFS rate was 50% at 2 years. Patients with non-MF/SS PCTCLs had 67% 2-year PFS. For all patients, the 5y-OS rate was 85% with a median OS of 2 years (confidence interval [CI], 0–18). For MF, the OS was 7.5 years (CI, 5–10); for SS, the OS was 1.8 years (CI, 0–6); and for non-MF/SS group, the OS was 2 years (CI, 1–18). The 2-, 5-, and 10-year OS rates in patients with MF were all 100%. For SS patients, the 1-, 2- and 5-year OS rates were 66%, 67%, and 0%, respectively. Patients with non-MF/SS PCTCLs had 100% 1-year OS and 100% 2-year OS. Disease progression to a higher clinical stage occurred in 6 patients (42.9%). Regarding the skin radiation dose, OS did not achieve statistical significance, and PFS showed marginal benefit ($p = 0.044$) with a trend for mid to conventional radiation doses. During dermatological follow-up examinations, 6/14 patients

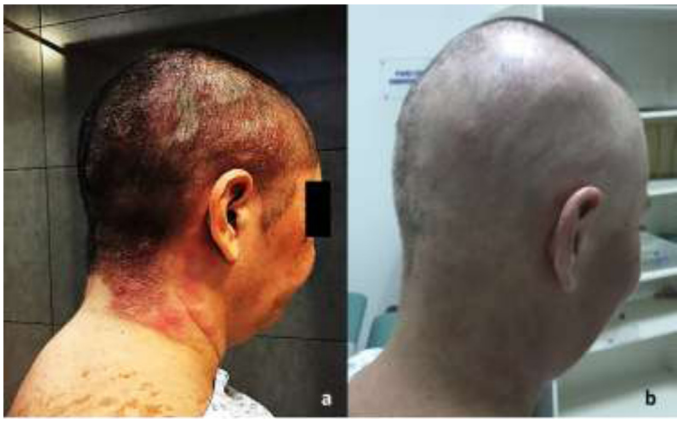

Fig. 4. a. Patient with Primary cutaneous peripheral T-cell lymphoma, not otherwise specified before starting TSEBT. Fig. 4**b.** The same patient 1 month after finishing middle-dose TSEBT. Abbreviations: TSEBT, total skin electron beam therapy.

Table 3
Characteristics of TSEBT.

	Whole Cohort n = 14 (%)	Standard Dose 36 Gy (%)	Intermediate Dose 24 Gy (%)	Low Dose 12 Gy (%)
Gender				
Male	6	0	0	6
Female	8	2	1	5
Complimentary				
Boost Radiation	7	0	1	6
Yes	7	0	0	7
No				
Skin Toxicity[a]				
Grade 1	10	1	1	8
Grade 2	4	0	0	4
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Response to TSEBT				
Complete	6	1	1	4
Partial	6	0	0	6
No Response	2	0	0	2
Recurrence				
Yes	6	2	1	3
No	8	0	0	8
Reirradiation for				
Recurrence	2	0	0	2
Yes	12	1	1	10
No				
Type of Radiation for Recurrence				
	1	0	0	1
TSEBT	1	0	0	1
Skin Directed (localized)				

[a] Skin toxicity was assessed using the Common Terminology Criteria for Adverse Events. Abbreviation: TSEBT, total skin electron beam therapy.

(42.9%) developed recurrence/progression. The median time to skin progression was 6 months (range, 3–25 months), with no significant difference regarding radiation doses. Overall, 5 patients died, and 4 deaths (28.6%) were attributed to SS.

4. Discussion

PCTCLs are a heterogeneous group of lymphoproliferative disorders with a variable clinical spectrum. It ranges from indolent patches and plaques to erythroderma and systemic involvement.[2] A variety of treatment modalities are available to the treating clinician. The choice of treatment should be based upon disease factors such as clinical subtype, stage, and tumor burden as well as patient factors, including age, comorbidities, and availability of therapeutic options.[5]

RT has been an important treatment option in the management of PCTCLs for over 50 years. It was first used and reported by Trump *et al.*[14] in 1953. Since then, several reports have demonstrated a correlation between disease-free interval and radiation dose. The efficacy of conventional-dose (30 Gy–36 Gy) has been published in several retrospective studies with ORRs ranging from 94.7% to 100%. The higher the dose, the better the response.[15–17] Several retrospective series over the past 25 years involving large cohorts have consistently shown the efficacy of conventional-dose TSEBT (i.e., 30 Gy–36 Gy) in various stages of MF/SS.[18,19] In 2011, Stanford's long-term experience with 36 Gy TSEBT was updated.[20] All patients demonstrated clinical improvement while 60% demonstrated CR. In our cohort, the two patients treated with 36 Gy had a mean response of 20 months.

Low-dose TSEBT is now widely used because of the opportunity for retreatment. The Stanford University experience treating MF patients with low-dose TSEBT ranging from 5 Gy to 30 Gy was reported.[21] ORR per dose group were 90%, 98%, and 97% in the 5–10 Gy, 10–20 Gy, and 20–30 Gy dose groups, respectively. CR rates were 16%, 35%, and 34% among patients treated with 5–10 Gy, 10–20 Gy, 20–30 Gy, respectively. There was no significant difference in PFS or OS among the dose groups. In other study by Kamstrup el al,[22] low-dose TSEBT with 10 Gy scheme was analyzed with an ORR of 95%, duration of response of 6 months, and 1–2 acute toxicity in 60% of patients. Hoppe et al. evaluated the efficacy and tolerability of low-dose 12-Gy TSEBT. The achieved ORR was 88%, with a clinical benefit of 18 months. Nine of 33 patients had a complete response.[23] Elsayad et al. retrospectively evaluated 45 patients with PCTCL treated with low-dose TSEBT (<30 Gy) or conventional-dose TSEBT (>30 Gy). They did not find higher or longer clinical benefit with conventional-dose TSEBT.[24,25] Kroeger et al. retrospectively evaluated the toxicity of TSEBT in 60 patients irradiated with conventional-dose (30 Gy) and low-dose TSEBT (12 Gy). Patients treated with low-dose TSEBT had significantly fewer grade 2 adverse events than those with conventional-dose regimens (33% vs. 79%, $p < 0.001$).[26]

Recently, the experience of the Roswell Park Institute using low-dose and conventional-dose radiation was published.[27] ORR was 100% in both groups, with a CR of 38% in the conventional-dose group and 25% in the low-dose group. There was no difference in OS or PFS between the two groups. Another retrospective French study with 26 patients with MF treated with low-dose and intermediate-dose TSEBT[28] showed an overall skin response rate of 96.2% (92.9% intermediate-dose and 100% low-dose group) with a median duration of response of 5 months, without significant difference between RT dose schemes. In the present study, there was no significant difference in OS among the dose groups and even when the PFS was marginally significant ($p = 0.044$) with a trend towards improved treatment response with middle and conventional-dose TSEBT, the borderline significance can be potentially explained by the pathological variant distribution among treatment groups and overall small number of patients. Quality of life information was recently published by Elsayad et al. in 44 patients receiving low-dose TSEBT. Life quality assessments showed significant reduction in patient symptoms and improvements in the emotional, social, physical, and functioning domains after TSEBT. A longer PFS was observed in patients who received maintenance or adjuvant treatments.[29]

This study reinforces the role of TSEBT when compared with other treatments and novel agents. Given our study's retrospective nature, it is not without limitations and biases. Patients with multiple histologies, radiation doses and stages were included. Another limitation of the current study is that immunophenotyping data was not investigated due to the retrospective nature. Considering this study is based on 14 patients only, further studies are necessary before a definitive conclusion can be reached. Longer follow-up of patients receiving low-dose TSEB is needed to assess the long-term efficacy and late toxicities of this scheme, in comparison to standard radiation dose.

5. Conclusions

Cutaneous lymphomas are extremely radiosensitive, and radiation treatment continues to occupy an important place in the management of PCTCLs. In our study, patients treated with TSEBT had an ORR rate of 85% and a median PFS of 6 months. Unfortunately, TSEBT is not widely available, and experience with this technique is limited. Randomized clinical data to directly compare distinct dose regimens are needed.

Conflict of interest

None.

Financial disclosure

None.

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