Total Skin Electron Beam Therapy as Part of Multimodal Treatment Strategies for Primary Cutaneous T-Cell Lymphoma

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Keywords

Radiotherapy · Total skin electron beam therapy · Mycosis fungoides · Sézary syndrome · Skin-directed · Systemic therapy · Immunotherapy

Summary

Total-skin electron beam therapy (TSEBT) is one of most effective treatments that has been used for cutaneous T-cell lymphoma. Low-dose TSEBT regimens (10–12 Gy) appear to be an effective alternative to conventional-dose TSEBT (30–36 Gy), yielding short-term remission of cutaneous manifestations with minimal toxicity. TSEBT can be administered to patients any time after a diagnosis of mycosis fungoides (MF). Patients requiring rapid relief from cutaneous lesions or symptoms may particularly benefit from TSEBT as an initial therapy. Radiotherapy (RT) dose, boost radiation delivery, maintenance treatment, and radiation tolerability may enhance remission rates and improve relapse-free survival following TSEBT. In addition, salvage local RT or TSEBT may be safely applied with high effectiveness. In this review, we focus on the use of TSEBT in patients with several forms of primary cutaneous T-cell lymphoma, and highlight the potential of low-dose TSEBT as part of a promising therapeutic approach.

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Introduction

Primary cutaneous T-cell lymphoma (pCTCL) is a heterogeneous group of non-Hodgkin's lymphomas that represents more than

two thirds of cutaneous lymphomas with an incidence of approximately 0.77 per 100,000 person-years at diagnosis [1]. Although a variety of mechanisms, genetic factors, and signaling pathway dysregulations have been reported in association with pCTCL, the etiology of pCTCL is still unclear [2]. Histopathologically, cutaneous manifestations of pCTCL are characterized by clonal proliferation of skin-homing malignant T lymphocytes and natural killer cells [3]. Severity of pCTCL has been determined with molecular diagnostic studies, immunohistochemistry, and flow cytometry, in addition to characteristic genetic features which can be detected in most cases [2–4].

Mycosis fungoides (MF) and Sézary syndrome (SS) together represent approximately 65% of all pCTCL cases [3]. MF, which is classified as an indolent non-Hodgkin's lymphoma, occurs mainly in men (62%) and usually in middle age or later [5]. Commonly, patients with early-stage MF present with pruritic patches and plaques, whereas patients with advanced-stage MF present with cutaneous tumors or erythroderma. SS is a leukemic variant of MF characterized by generalized cutaneous, lymph node, and blood involvement [3]. The International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC-CLTF) revised the staging system for pCTCLs in 2007 to incorporate recent advances in diagnostic techniques and tumor cell biology and to standardize evaluation and management across treatment centers [4, 6]. Most patients present with early-stage disease and thus have a good prognosis and can be optimistic for long-term survival [5, 7]. The most common causes of pCLCT-related death are immunosuppression and opportunistic infections [2]. Radiotherapy (RT) is the most effective single modality treatment for MF [8]. The duration of cutaneous remission following total skin electron beam therapy (TSEBT) may be influenced by the delivered RT dose, boost radiation, maintenance treatment, radiation tolerability, and disease stage [9, 10].

Current Therapeutic Options for pCTCL

Recently published national and international treatment guidelines are used to inform treatment selection on the basis of patients' clinical condition and tumor stage [7, 11–14]. Many topical and systemic therapies have been developed in recent decades. The most commonly used skin-directed therapies are topical steroids, psoralen plus ultraviolet A (PUVA), ultraviolet B, mechlorethamine (a.k.a. nitrogen mustard), carmustine, topical retinoid, and RT. Systemic therapies include oral retinoid, single or multi-agent chemotherapy, steroids, interferon (IFN), extracorporeal photopheresis (ECP), and histone deacetylase (HDAC) inhibitors [7, 11, 15–17]. Combinations of topical and systemic modalities have been explored [16]. In addition, some novel agents and immunotherapies have been reported to have efficacy for the treatment of advanced MF and SS [11, 16, 18, 19]. Finally, allogeneic hematopoietic stem cell transplantation (AH SCT) has emerged as a feasible modality in patients with advanced pCTCL [20, 21].

RT was first employed by Scholtz to treat MF in the early 1900s [22], and TSEBT has been used to treat CTCL since 1951 [23–25]. TSEBT, which capitalizes on the radiation sensitivity of MF, has been well studied, though it remains a very specialized treatment that is not widely available. Palliative low-dose RT has yielded favorable results, even with doses ≤ 10 Gy, with an overall response rate of approximately 90% [8, 25–27]. Because relapses occurred following low-dose RT, the radiation doses used have been gradually increased up to 36 Gy to obtain a longer-term clinical benefit; however, this more intensive regimen has been associated with significant treatment-related skin toxicities and late relapses [8, 28]. Low-dose TSEBT regimens, alone or in combination with other treatments, have been gaining interest recently with the hope of minimizing the risk of adverse events (AEs) and the possibility for repetition in the event of relapse [8, 9, 29–31]. Pre- or post-TSEBT local RT for tumorous lesions, enlarged lymph nodes, and underdosed sites has been recommended to minimize the risk of local relapse [13].

The aim of this review is to highlight the place of TSEBT in the framework of current recommendations and to present promising therapeutic approaches for different forms of pCTCLs (table 1).

MF

According to current treatment guidelines, treatment options for MF include skin-directed therapies or local RT and TSEBT (table 2). Most patients with early-stage MF can be treated primarily with skin-directed therapy. There are no randomized trials supporting selection of radiation-based therapies over other therapies [16].

In early-stage (T1, T2) disease, ultraviolet B phototherapy and PUVA therapy result in complete response rates (CRRs) of 81 and 71%, respectively [32]. Adjuvant IFN or retinoids following PUVA may be more effective and tend to prolong relapse-free survival (RFS) [16, 33, 34]. Topical corticosteroids achieve CRRs of only 63% in T1 stage and 25% in T2 stage, with most of the responsive patients developing early relapses [35]. Although chemotherapeu-

tic mechlorethamine has been found to have good efficacy, it is not widely available outside the US [16].

In refractory early-stage and advanced-stage disease, systemic approaches are mandatory [16]. Commonly, immunomodulatory therapies (i.e. ECP, IFN, retinoids) are used. ECP achieves an overall response rate (ORR) of up to 64% and a CRR approaching 25% [36]. Retinoids have been used in pCTCL for over 2 decades with an ORR reaching 75% and minimal CRR ($< 32\%$). The most common retinoid currently in use is bexarotene, a synthetic retinoid that activates retinoid X receptors selectively, thereby regulating cellular differentiation, proliferation, and apoptosis. Various retinoid combination treatments have been studied, though there has been no evidence of synergistic activity improving response rates [37]. Combined retinoid and IFN treatment has been administered safely in pCTCL [38]. Low-dose methotrexate, with or without IFN, can be effective for patients with refractory early-stage disease [16].

In terms of novel agents, the proteasome inhibitor bortezomib was reported to result in an ORR of 70% and a CRR reaching 17% [18, 79]. The ORRs associated with pralatrexate and forodesine were in the range of 43–55%, with CRRs not exceeding 22% [18]. Human recombinant interleukin 12 has also been demonstrated to produce short-term partial remission (progression-free survival (PFS) 2 months) in 43% of patients with early-stage MF [39], while a combination of bexarotene and denileukin diftitox has been advanced as a reasonable option for patients with advanced disease [2]. Minimal efficacy of HDAC inhibitors, such as vorinostat or romidepsin, and immunomodulatory agents, such as lenalidomide, for pCTCL has been shown (ORRs of approximately 35%) [18]. Other HDAC inhibitors currently being investigated include entinostat, belinostat, panobinostat, AN-7, and quisinostat [2]. In situ vaccination against MF by intratumoral injection of a Toll-like receptor agonist combined with ultralow-dose local RT (4 Gy) seems to be feasible (ORR 35%) with acceptable toxicities [19].

TSEBT Technique

The 'six-dual-field' or modified Stanford technique is commonly used to deliver TSEBT [24, 40]. During irradiation, patients stand in an upright position on a static base. The rotational TSEBT technique has also been successfully used in some studies [10, 41]. Electron beams with 6–9 MeV are usually used (depending on the depth of skin infiltration) to treat 3 anterior and 3 posterior treatment fields, each having a superior and inferior portal with beam angulations. The radiation treatment typically takes 20–30 min per day. Supplementary radiation to the medial thigh, plantar surfaces, perineal, scalp, and other areas may be planned to compensate for underdosing in these regions based on thermoluminescent dosimeter measurements or according to clinical findings.

TSEBT Results

Among tested pCTCL treatment modalities, RT has achieved the highest ORR (Table 2). In a retrospective study by Kim et al. [43],

Table 1. Total skin electron beam therapy (TSEBT) in combination with other modalities for mycosis fungoides (MF)/Sézary syndrome (SS)

Study [ref.]	Patients (m/f), n	Age, median (range), years	Clinical stage (n)	Follow-up, median (range)	Previous treatment	RT type	Adjuvant treatment	CR, %	RFS/DFS/FFR	OS
Van Vloten et al., 1985 [53]	40 (32/8)	24–82	I+II (30)	57 months (4–116)	n.a.	TSEBT ^a (28–35 Gy/10 weeks)		90	69% (FU)	70% (5-year)
Bravermann et al., 1986 [26]	92 (49/43)	n.a.	III (10) I (26) II (35) III (16) IV (15)	up to 15 years	n.a.	74 TSEBT ^a (36 Gy/9 weeks) 18 TSEBT ^a (6–16 Gy)	10/40 poly-CTX 50/92 poly-CTX – –	80 98 (ORR)	70% (FU) CM prolongs DFS in T1–2 MF (60 vs. 25%)	OS benefit with high-dose TSEBT in T1–2 MF (80 vs. 40 %)
Kim et al., 1996 [43]	122 (75/47)	49 (19–81)	IA – T1N0M0	9.8 years (0.5–30.5)	n.a.	32 TSEBT ^a 73 NM		97 68	58.7/58.7% (5-/10-year FFR) 52/45% (5-/10-year FFR)	87% (10-year) 87% (10-year)
Wilson et al., 1995 [52]	163	59 (20–88)	T1 (36) T2 (65) T3 (41) T4 (21)	44 months (2–179)	n.a.	10 TSEBT ^a 4 local RT TSEBT ^a (36 Gy/9 weeks)	+ NM 97/163 adjuvant therapy (83 poly-CTX, 14 ECP)	97 87 78 61	65% (5-year) 50% (5-year) 17% (5-year) 24% (5-year)	90% (5-year) 83% (5-year) 50% (5-year) 48% (5-year) OS benefit with adjuvant ECP in T3 and T4 MF ($p < 0.06$)
Quiros et al., 1997 [42]	114 (69/45)	58 (20–88)	T1 (39) T2 (75)	62 months (3–179)	n.a.	TSEBT ^a (36 Gy at 1-Gy fx, 4 fx/week)	6/39 PUVA 33/39 no PUVA 8/75 PUVA 67/75 no PUVA	97 87	median DFS: > 103 vs. 66 months ($p < 0.01$) median DFS: > 60 vs. 20 months ($p > 0.03$)	100 vs. 82% (5-year) ($p < 0.1$)
Wilson et al., 2000 [61]	44 (29/15)	68 (29–82)	T4 (44)	2.2 years (0.3–13.9)	other therapies (73%)	TSEBT ^a (32–40 Gy/9 weeks) ± ECP (17/44)	21/44 ECP 23/44 no ECP	74 71	93/83% (2-/3-year DFS) 49% (2-/3-year DFS)	88/58% (2-/3-year) 63/56% (2-/3-year)
Ysebaert et al., 2004 [58]	57 (31/26)	61 (19–84)	T1 (24)	114 months (14–300)	44% received topical therapy	TSEBT ^a (30 Gy/4 weeks)	31 relapses (12/31 TSEBT; 6/31 local RT; 13/31 other topical or systemic agents)	87.5 (3 months) 84.8 (3 months)	75% (5-year RFS for primary Rx) 100% (5-year RFS salvage Rx)	89% (10-year) 50% (10-year)

Table 1. Continued on next page

Table 1. Continued

Study [ref.]	Patients (m/f), n	Age, median (range), years	Clinical stage (n)	Follow-up, median (range)	Previous treatment	RT type	Adjuvant treatment	CR, %	RFS/DFS/FFR	OS
Chinn et al., 1999 [47]	148 (89/59)	58 (19–87)	T2 (109)	83 months (5–324)	-	TSEBT ^a (36 Gy)	± NM	76	90/60% (1-/5-year FFR)	72/53% (5-/10-year)
							NM alone	39	40/30% (1-/5-year FFR)	68/56% (5-/10-year)
			T3 (39)			TSEBT ^a (36 Gy)	± NM	44	30/15% (1-/5-year FFR)	44/28% (5-/10-year)
							NM (+ 10 local RT 10–15 Gy)	8	10/10% (1-/5-year FFR)	66/56% (5-/10-year)
Navi et al., 2011 [44]	180 (110/70)	57 (19–87)	T2 (70/103)	77 months (19–86)	1–9 topical/ systemic Rx	TSEBT ^a (30–40 Gy/ 8–10 weeks)	-	72	8.9 years (PFS)/2.4 years (FFR)	11.3 years
			T3 (69/77)				43/70 NM	77	8.5 years (PFS)/2.7 years (FFR)	10.9 years
							-	44	1.8 years (PFS)/1.0 years (FFR)	4.2 years
							42/69 NM	48	2.9 years (PFS)/0.8 years (FFR)	3.9 years
Lindahl et al., 2011 [49]	35 (23/12)	66 (41–85)	T1 (0/2)	7.6 months (3 days to 3.7 years)	97% topical Rx	TSEBT ^a 30 Gy (25)	96% received	68	72% (1-year FFP)	n.a.
Kamstrup et al., 2008 [70]			T2 (9/5)		77% systemic therapy	TSEBT 4 Gy (10)	adjuvant Rx	20	20% (1-year FFP)	n.a.
Heumann et al., 2014 [10]	68 (35/33)	52 (18–89)	T2 (18)	61 months	n.a.	rotational TSEBT (30–36 Gy/9–12 wk)	38% received	88	14 months (RFS)	> 55 months
			T3 (37)				adjuvant therapies	83	10 months (RFS)	91 months
			T4 (13)				longer RFS with adjuvant Rx (<i>p</i> = 0.013)	69	12 months (RFS)	59 months
Elsayad et al., 2015 [9]	45 (31/14)	63 (41–84)	MF/SS (9 T2, 14 T3, 13 T4)	27 months 8.5 months	1–8 topical/ systemic Rx	24 TSEBT ^a 30–36 Gy	71% received	63	15 months	77 months
						12 TSEBT ^a < 30 Gy	87% received boost RT	25	6 months	16 months
			non-MF/ SS (1 T2, 8 T3)			TSEBT ^a 30 Gy/3–4 weeks		78	33% (2-year EFS)	23 months longer OS with adjuvant Rx (<i>p</i> < 0.001)

^aSix-dual-field technique.

RT = Radiotherapy; CR = complete response; RFS = relapse-free survival; DFS = disease-free survival; FFR = freedom from relapse; OS = overall survival; ORR = overall response rate; EFS = event-free survival;

FU = follow-up; M = male; F = female; ECP: extracorporeal photopheresis; Rx = treatment; CTX = chemotherapy; TSEBT = total skin electron beam therapy; NM = nitrogen mustard; PUVA = psoralen plus ultraviolet A; n.a. = unknown; fx = fractions.

Table 2. Efficacy and toxicity rate of different treatments for mycosis fungoides/Sézary syndrome

Therapy [ref.]	Disease stage	ORR, median (range), %	CR, %	Toxicities (grades 3/4), %	Duration of responses or TTNT
Local radiotherapy [71]	T1	100	97	none	10-year: 85%
Topical steroids [35]	T1–2	90 (82–94)	49 (25–63)	none	6% relapse rate after median follow-up of 9 months (range 3–36)
PUVA and ultraviolet B [32, 72, 73]	T1–2	74–100	22–81	none	median 10–24 months (range 1–66)
Human recombinant interleukin 12 [39]	T1–2	43	0	13	median 2 months
Mechlorethamine [74]	T1–4	83	50	rare	median 12 months
Oral retinoid [37, 75]	T1–4	54–75	8–31	rare	median 7–16 months (range 1 to > 48)
Chemotherapies [55]	T1–4	25–80	11–22	common	median 4 months (range 2–6)
TSEB (low or high dose) [29, 44, 59]	T2–4	95 ^a	29–75 ^a	0–10 ^a	median 6–29 months ^a
ECP [36, 55]	T2–4	56 (32–62)	18 (9–28)	rare	median 9 months (6–13); 1-year: 39%
HDACi (i.e., vorinostat, romidepsin) [55, 76, 77]	T2–4	30–34	1.3–6	6	range 4.5–8 months
Toll-like receptor agonist [19]	T2–4	36	0	7	range 6–37 months
Immunotherapies [55, 63–66, 78]					
Brentuximab	T2–4	54–73	≤35	6–31	median 13 months
Mogamulizumab	T2–4	37	8	24–73	median 11 months
Zanolimumab	T2–4	56	9	4	median 20 months
Alemtuzumab	T2–4	51	18	62	median 3–4 months
Bortezomib [79]	T3–4	67	17	17	range 7–14 months

^aSeverity and adverse event rate vary according to radiation dose delivered.

ORR = Overall response rate; CR = complete response; TTNT = time to next treatment; PUVA = psoralen plus ultraviolet A; TSEB = total-skin electron beam therapy; ECP = extracorporeal photopheresis; HDACi = histone deacetylase inhibitor.

TSEBT lead to a CRR of 97% in patients with stage T1 disease, compared to 68% for mechlorethamine, with a higher RFS (10-year RFS rates 59 versus 45%, respectively; $p < 0.05$). However, this efficacy did not translate into a long-term survival benefit (10-year overall survival (OS), 87 and 87%; $p = 0.2$). In addition, TSEBT is a reasonable treatment option for patients with T2 and T3 disease owing to its penetration ability, which seems to be superior to that of mechlorethamine [44, 45]. TSEBT for T4 disease or SS remains controversial. However, cutaneous and peripheral blood improvement has been reported in 82 and 55% of patient groups, respectively. These findings indicate that antitumor immunity can be restored in addition to reducing tumor burden to minimal levels before AHST [46].

In terms of multimodal therapeutic approaches, delivery of neo-adjuvant, concurrent, or adjuvant therapy with TSEB remains controversial due to an inconsistency of findings across different treatment centers. Several studies (table 1) reported significant improvements in CRR, disease-free survival (DFS), and OS benefits following multimodal approaches. In patients with early MF (T1, T2), adjuvant PUVA therapy improved 5-year DFS significantly in comparison to non-PUVA adjuvant/no adjuvant therapy (85 vs. 50%; $p < 0.02$) [42]. Superiority of TSEBT with 8–36 Gy $\pm$ mechlorethamine for 16 months over mechlorethamine alone has been observed in T2 (CRR, 76 vs. 39%; $p = 0.03$) and T3 disease (CRR, 44 vs. 8%; $p < 0.05$), with longer RFS in patients who received adjuvant mechlorethamine therapy [47]. Similarly, Price et al. [48] reported a modest improvement with adjuvant mechlorethamine (37 vs. 29 months without mechlorethamine). However, no clinical advantage of adjuvant mechlorethamine (for 6 months) in com-

plete responders to TSEBT was observed after longer follow-up in T2 and T3 disease, perhaps due to the short duration of adjuvant mechlorethamine or the limited number of prior treatments [44]. Regarding previous therapies, a tendency to sustain TSEBT effectiveness in patients treated previously with mechlorethamine has been observed [49]. Combined TSEBT and IFN (for 1 year) is a feasible option, with increased but acceptable acute toxicity, though the addition of IFN did not improve outcome per se [50]. In contrast, a combination of conventional-dose TSEBT with concurrent oral retinoids has shown an acceptable toxicity profile without compromising either therapy [38, 51].

Single or multi-agent chemotherapy (i.e., methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, cyclophosphamide, vincristine, prednisone, or etoposide) can be considered in patients with extracutaneous involvement and results in CRRs ranging from 11 to 57%, while combined conventional-dose TSEBT (24–40 Gy) with chemotherapy can yield higher CRRs (23–88%) [17, 38] with a trend towards a survival gain [26, 52, 53]. In a randomized trial [54], TSEBT with 30 Gy combined with polychemotherapy was compared with topical therapy in 103 patients with MF. Although the combined therapy had a significantly higher CRR (38 vs. 18%; $p = 0.032$), DFS and OS were identical in the 2 groups [54]. Duvic et al. [38] analyzed the effectiveness of a multimodal approach including induction and maintenance therapies applied in sequence with TSEBT in 28 MF/SS patients. Among early-stage patients, the CRR was 94% (median RFS 18 months), whereas in stage III–IV patients, the CR was 64% (median RFS 5 months) [38]. Generally, combined modalities are well tolerated.

Fig. 1. Lesions in a patient with primary cutaneous aggressive CD8+ T-cell lymphoma. **A, B** Appearance before with mSWAT score of 116. **C, D** 6 weeks following total skin electron beam therapy (TSEBT; total dose of 24 Gy administered with 1 Gy daily fractions in 5 weeks) demonstrating complete remission of skin manifestations with grade 1/2 adverse events (hair loss and skin dryness). **E, F** 6 months following TSEBT showing localized skin relapses (mSWAT of 12); note hair growth and resolution of skin adverse events.

However, serious toxicities during intensive chemotherapy regimens have been reported [38, 54]. In a recent study by Hughes et al. [55], chemotherapy appeared to have a limited durability of disease control when compared with other therapies. The most recent consensus recommendations from EORTC-CLTF consider maintenance topical (i.e., cortisone, PUVA, UVB, mechlorethamine) or systemic therapies (i.e., low-dose methotrexate, IFN, retinoids, ECP) for MF/SS patients to improve/sustain the duration of clinical benefit [14].

In general, 30 Gy is considered for advanced disease, high percentage of tumors, or in the definitive setting prior to transplant. However, low-dose TSEBT (< 30 Gy) has been used to palliate skin manifestations of MF/SS with a reasonable remission rate [25, 56]. In a recent prospective phase II trial [29, 30] evaluating the efficacy of low-dose TSEBT with 10–12 Gy in MF (stage IB–IV), an 8-week median time to clinical response was observed. The ORRs were in the range of 88–95%, with a CRR of approximately 30% [29, 30]. Improvement in pruritus occurred in approximately 60% of the patients [29]. In addition, a reduction in disease burden may improve the ability to control any remaining disease with topical therapies [30]. Regarding the RFS, no significant difference between low-dose and conventional dose regimens could be detected [8, 9]. In a study conducted at the Stanford Cancer Center, Harrison et al. [8] found a similar ORR (approximately 98%) and CRR (approximately 35%) in patients treated with low-dose (10 to < 20 Gy) and medium-dose (20 to < 30 Gy) regimens [8]. An ultralow radiation dose (4 Gy/4 days), however, yielded a CRR ($p < 0.01$) and freedom from progression rate ($p < 0.01$) significantly less than those obtained with conventional-dose regimens [49].

TSEBT followed by AHSCT may represent a feasible treatment with long-term remissions in selected patients with advanced

pCTCL [20, 21]. In the case of skin relapse, salvage therapy with low-dose radiation-based therapies (local RT or TSEBT) can be conducted safely with a high ORR (90–100%) [44, 57, 58]. Other skin-directed or systemic salvage treatments have also been applied without loss of efficacy following TSEBT [8, 42, 43, 47]. Ysebaert et al. [58] found that salvage RT showed a DFS of 73%, while other salvage therapies had a DFS of 60%; however, this difference was not significant ($p = 0.3$).

TSEBT Toxicity

The most common AEs include fatigue, skin reaction, alopecia, nail ridging or loss, lower leg edema, xerosis, and ocular irritation. In our experience, all patients treated at the University Hospital of Munster report mild skin reactions, with a lower rate of grade 2 and grade 3 toxicities being observed with low-dose regimens (<30 Gy) compared to standard-dose regimens; these are almost always temporary (fig. 1). In addition, lower rates of skin infections have been reported with low-dose regimens [30, 59]. Table 2 presents an overview of efficacy and toxicity rates of different treatment modalities for MF/SS in comparison with TSEBT.

Variants and Subtypes of MF

Although treatment experience is limited and most patients are less responsive to skin-targeted therapies, relative to classical MF, RT may be recommended [3, 9, 30]. Surgical excision, topical mechlorethamine, or topical steroids may be an alternative in some patients with granulomatous slack skin or pagetoid reticulosis [3].

In follicutropic MF, Van Doorn et al. [60] found that TSEBT achieved higher CRR than PUVA (54 vs. 5%). However, the duration of remission was quite short, which may be controlled effectively by a maintenance therapy [60]. In addition, low-dose TSEBT (12 Gy) seems to be effective for patients with follicutropic MF (ORR 87%, CRR 37%) and large cell transformation (ORR 100%, CRR 25%) [30].

Erythrodermic MF and SS

ECP, with or without IFN- α , has been reported to be an effective treatment for erythrodermic MF and SS, with ORRs of up to 90% (CRR approximately 25%). Beneficial results with IFN (with or without PUVA) in combination with low-dose chlorambucil and prednisone or with methotrexate, retinoids, and alemtuzumab (an anti-CD52 monoclonal antibody) have also reported [3, 17, 34, 36, 61]. TSEBT as part of a therapeutic regimen seems to be effective in erythrodermic MF and SS; however, few patients sustain long-term cutaneous remission [9, 29, 38, 49, 52, 61, 62]. TSEBT also has a beneficial systemic effect in terms of reducing tumor burden in the peripheral blood in SS patients [46]. A combination of TSEBT and ECP (for 6 months) resulted in a CRR of 74% in patients with erythrodermic MF, with a significant improvement in DFS and cause-specific survival [61]. In SS, combined immunomodulatory therapy, targeted biologic agents, or TSEBT followed by AHST represent promising options with 4-year PFS rates reaching 52% [20, 21].

Non-MF/SS

Due to the rarity and heterogeneity of non-MF/SS-type pCTCL, there are no established classification or standard treatment recommendations for these patients. Owing to the aggressiveness of most histologic entities of non-MF/SS, most affected patients require chemotherapy as their initial treatment [3]. For solitary or localized lesions, RT or surgical excision can be applied [3]. Patients with extracutaneous disease or rapidly progressive skin disease require systemic chemotherapy (doxorubicin-based multi-agent chemotherapy) with or without HSCT [3]. Studies exploring RT use for other forms of pCTCL are lacking; therefore, RT options should be decided individually based on multidisciplinary discussions. In this context, TSEBT has been used effectively in patients with refractory multifocal skin lesions [9, 49].

Future Perspective

Modern immunotherapeutic approaches (i.e., monoclonal antibodies, transimmunization, and customized vaccines) have been explored [19]. Our understanding of pCTCLs is evolving as ongoing research continues to improve our comprehension of the molecular mechanisms underlying malignancy. Such research may

enable the development of effective targeted treatment approaches for defined subgroups of patients.

Regarding immunotherapies, the anti-CD52 monoclonal antibody alemtuzumab has been demonstrated to have efficacy in patients with pCTCL (ORR 51%, CRR 18%) [18, 78]. A recent phase II clinical trial showed moderate efficacy of the anti-CD30 monoclonal antibody brentuximab vedotin, the anti-CCR4 antibody mogamulizumab, and the anti-CD4 antibody zanolimumab in pCTCLs as monotherapies, with ORRs reaching 73% (median PFS 13 months), 37% (median PFS 11 months), and 56% (median PFS 20 months), respectively [63–66]. In comparison to standard-of-care options (methotrexate or bexarotene), brentuximab vedotin provides a higher ORR (56 vs. 13%; $p < 0.001$) and PFS (16.7 vs. 3.5 months; $p < 0.001$) in CD30-expressing pCTCL [67]. A clinical investigation of the new anti-PD1 antibody nivolumab showed that the agent had good tolerability in patients with recurrent or refractory MF with an ORR of 15% [68]. Preliminary phase I results with the novel targeted immune therapy IPH4102 (an anti-KIR3DL2 monoclonal antibody) showed excellent tolerability in advanced pCTCL patients [69]. Additional studies of these modern immunotherapy approaches in pCTCL are ongoing.

Despite the minimal toxicity profiles of low-dose TSEBT and immunotherapy for MF/SS, combined approaches to enhance RT efficacy or prolong duration of remission/clinical benefit do not yet exist. There are ongoing clinical studies evaluating the toxicity and efficacy of brentuximab combined with 12 Gy TSEBT (phase I trial, ClinicalTrials.gov NCT02822586) and analyzing the toxicity profile of recombinant interleukin-12 combined with 12 Gy TSEBT (phase II trial, ClinicalTrials.gov NCT02542124). Additionally, another phase II study of low-dose TSEBT combined with 12 Gy with or without 1 year of weekly maintenance therapy with mechlorethamine gel was registered recently (ClinicalTrials.gov NCT02881749).

Conclusion

Due to the rarity of pCTCL, randomized clinical trials comparing different treatment modalities are lacking. TSEBT has been found to be an efficacious treatment modality for several forms of pCTCL at several radiation doses and can be recommended for curative or palliative intent. In addition, TSEBT may be administered to patients at any time point after diagnosis of MF. That being said, patients requiring rapid relief from cutaneous lesions or symptoms particularly benefit from TSEBT as an initial therapy.

Treatment availability is an important factor in treatment decisions. Combined and/or maintenance therapy administration following TSEBT may prolong the duration of disease remission and warrants further investigation. Trends are moving towards short-course low-dose TSEBT regimens with, so far, good clinical results. Because of the high efficacy of TSEBT and the highly dynamic field of immunotherapy, specialized academic institutions should collaborate with hospitals in the treatment of pCTCLs to provide access to these therapeutic options and to evaluate the effectiveness of combined approaches in randomized trials.

Disclosure Statement

The authors declare no conflict of interest.

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