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REVIEW

Advances in classification and treatment of primary cutaneous lymphomas

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Abstract

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of extranodal non-Hodgkin lymphomas, characterized with skin involvement as the primary or predominant manifestation. While early-stage PCLs typically have a favorable prognosis, managing patients with aggressive progression or advaced stages remains a challenge. Recent advancements in molecular biology and sophisticated clinical laboratory tests have significantly improved the classification and management of PCLs, which provide more targeted and effective treatment strategies for patients. This review summarizes the latest classification schemes and therapeutic options for PCLs, with a focus on the latest developments and future directions in the field.

Keywords Primary cutaneous lymphoma · Prognosis · Targeted therapy · Classification

Introduction

Primary cutaneous lymphomas (PCLs) constitute a highly diverse group of malignancies, posing significant challenges in both diagnosis and treatment. PCLs primarily originate from mature T and B lymphocytes, with less frequent cases originating from NK cells [1]. These lymphomas are distinct due to their predominant infiltration into the skin, which necessitating a high level of clinical acumen to accurately identify their most prevalent presentations and facilitate differential diagnosis. The clinical manifestations of PCLs are notably diverse, complicating the development of standardized diagnostic and therapeutic strategies. However, recent advancements in understanding the molecular and signaling pathways involved in PCL pathogenesis have led to the emergence of innovative and personalized treatment modalities. This growing knowledge has promoted a broad consensus and provided more consistent diagnostic and treatment approaches for PCL patients.

For patients with early-stage primary cutaneous T-cell lymphoma (CTCL), skin-directed treatments (SDT) are preferred, encompassing topical corticosteroids, nitrogen mustard, bexarotene, imiquimod, phototherapy, and superficial radiotherapy [2]. In contrast, systemic treatments are necessary for advanced stages patients, including targeted therapy, immunotherapy, and chimeric antigen receptor T-cell (CAR-T) therapy [2]. For primary cutaneous B-cell lymphomas (CBCL) with isolated lesion, the first-line treatment is local radiotherapy or single resection [3]. For individuals diagnosed with systemic disease, rituximab in combination with chemotherapy is considered the first-line treatment [3]. CBCL patients with widespread, recurrent, or refractory disease may benefit from emerging new treatment strategies.

This article reviews the latest classification and treatments of PCLs, emphasizing novel therapeutic approaches such as targeted therapies, immunotherapies, and cutting-edge treatment options currently being explored in the field.

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Classification of PCLs

In 2005, a consensus classification for PCLs was released by the European Organization for Research and Treatment of Cancer (EORTC) in collaboration with the World Health Organization, which was subsequently updated in 2018 [4]. Approximately 75% of all PCLs are classified as CTCL, while CBCL accounts for the remaining 25%. Furthermore, both CTCL and CBCL can be further categorized according to clinical features, histopathological findings, and biomolecular characteristics (Table 1) [4].

CTCL

Mycosis fungoides (MF), variants of MF, and Sézary syndrome (SS)

MF is recognized as the most common type of CTCL, representing approximately 60% of CTCL cases and nearly 50% of all PCLs [5]. The WHO-EORTC classification includes not only the classic Alibert-Bazin type of MF but also three distinct variants: folliculotropic MF (FMF), pagetoid reticulosis (PR), and granulomatous slack skin (GSS) [6]. Moreover, several other clinicopathological subtypes of MF have been described, such as hypopigmented, hyperpigmented, and psoriasiform MF. Despite the distinct clinical and pathological characteristics of these subtypes, they are grouped under the classic MF category because of their analogous prognosis [6]. Classic MF comprises 88.6% of MF cases, while FMF accounts for 11.4%. Pagetoid reticulosis and GSS are extremely rare, less than 1% of MF cases in total [4].

Classic MF is an indolent disease with infiltration of neoplastic CD4+T cells into the skin. Early lesions lack histopathological specificity, and patients typically experience patch, plaque and tumor stages [7]. In histopathology, classical MF is characterized by a dermal lymphocyte infiltration zone with atypical epidermal and dermal lymphocytes, usually arranged in a basal pattern. Pautrier's microabscesses are observed in a small number of cases, particularly during the initial stages of MF, which are useful but not specific diagnostic features [8]. The characteristic of plaque MF is the irregular enlargement of epidermal lymphocytes in the

Table 1 Subclassifications of primary cutaneous lymphomas

Primary cutaneous T-cell lymphomas (CTCL)	Primary cutaneous B-cell lymphomas (CBCL)
Classic mycosis fungoides (MF) MF variants Folliculotropic MF (FMF) Pagetoid reticulosis (PR) Granulomatous slack skin (GSS)	Primary cutaneous follicle center lymphoma (PCFCL)
Sézary syndrome (SS)	Primary cutaneous marginal zone lymphoma (PCMZL)
Adult T-cell leukemia/lymphoma(ATL)	Primary cutaneous diffuse large B-cell -lymphoma, leg type (PCDLBCL, LT)
Primary cutaneous CD30-positive lymphoproliferative disorders (PC CD30+LPD) Primary cutaneous anaplastic large cell -lymphoma (PCALCL) Lymphomatoid papulosis (LyP)	EBV-positive mucocutaneous ulcer (EBVMCU)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	Intravascular large B-cell lymphoma (IVLBCL)
Extranodal NK/T-cell lymphoma, nasal type(ENKTL)	
Chronic active EBV infection (CAEBV)	
Primary cutaneous peripheral T-cell -lymphoma, rare subtypes Primary cutaneous gamma-delta T-cell -lymphoma (PCGDTCL) Primary cutaneous CD8-positive aggressive-epidermotropic cytotoxic T cell -lymphoma (PCAECTCL) Primary cutaneous CD4-positive -small/medium T-cell lymphoproliferative -disorder (CD4+SMTCLPD) Primary cutaneous acral CD8+T-cell -lymphoma	
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified	

nucleus, which appear as bands in the dermis and are associated with dense "linear" fibrosis [2]. The malignant cells typically express CD3+, CD4+, CD45RO+, with deletion of CD7 and/or CD26 [9].

FMF is a distinct variant of MF, defined by the infiltration of atypical T cells into hair follicles rather than the epidermis [6]. The immunophenotype of FMF is similar to classic MF, typically CD4 + and CD7- [10]. Clinically, FMF presents as acneiform lesions, plaques, or tumors, predominantly on head and neck [6]. FMF is usually associated with poor prognosis, with a 5-year overall survival rate (OS) of 75%, lower than classical MF, which is mainly due to the deep impact of FMF on the skin, making it more resistant to traditional treatments [10].

Pagetoid reticulosis represents a rare and chronic MF, marked by resemble psoriasis or show hyperkeratosis on the extremities,,which can be effectively treated with local therapies [6]. The epidermis exhibits hyperplasia with a pagetoid pattern of atypical T-lymphocytes [6]. GSS is another rare variant of MF, presenting as lax skin with granulomatous inflammation on axillae and groin. GSS is distinguished by a dense, granulomatous infiltrate in the dermis, composed of atypical T-lymphocytes intermingled with histiocytes, multinucleated giant cells, and eosinophils [10]. The prognosis of GSS is typically more favorable compared to other aggressive forms of MF. However, patients with GSS face an elevated risk of developing secondary hematologic malignancies, such as anaplastic large cell lymphoma or Hodgkin lymphoma [6].

SS is an aggressive variant of CTCL with poor prognosis, which is characterized by erythroderma, widespread lymph node enlargement, and the presence of malignant T-cells in the peripheral blood [11]. While SS shares a similar immunophenotype with MF, it is distinguished by a more significant reduction of pan-T-cell markers, a higher CD4/CD8 ratio, and significant blood involvement [12–13].

Adult T-cell leukemia/lymphoma (ATL)

ATL is an aggressive mature T-cell malignancy associated with human T-lymphotropic virus type 1(HTLV-1) positivity, lymphadenopathy, organomegaly, hypercalcemia, and high LDH levels. Skin involvement of ATL is common, occurring in approximately half of all patients [14–16] Additionally, skin involvement is considered as a distinct prognostic factor [17]. The immunophenotype of ATL cells is generally characterized by the presence of CD2, CD3, CD4, and CD25 [14].

Primary cutaneous CD30-positive lymphoproliferative disorders (PC CD30 + LPD)

PC CD30 + LPD encompasses two distinct entities: primary cutaneous anaplastic large cell lymphoma (PCALCL) and lymphomatoid papulosis (LyP) [4], accounting for 30% of CTCL cases [18]. Although both LyP and PCALCL are characterized by medium to large atypical CD30 + neoplastic T-cell infiltration, they differ significantly in clinical presentation, disease progression, and overall prognosis [19].

PCALCL

PCALCLis defined by dermal infiltration of medium to large anaplastic cells, potentially extending into the subcutaneous tissue [20]. Immunohistochemical analysis typically shows strong CD30 positivity [21, 22]. The differential diagnosis includes type C LyP, CD30 + MF with large cell transformation (LCT), systemic ALK-negative anaplastic large cell lymphoma (ALCL) with skin involvement [23–25].

LyP

LyP typically presents as red-brown nodules or papules that grow to the size of a pea, often developing hemorrhage and ulceration within 3 to 4 weeks before spontaneously regressing [26, 27]. Histopathologically, LyP exhibits considerable variability and is classified into six major subtypes based on their morphological and immunophenotypic characteristics: types A, B, C, D, E, and *DUSP22* rearranged [4], which are crucial to understand the clinical behavior of the disease.

LyP type A is the classic and most prevalent form, representing approximately 47.2–82% [28]. It is characterized by large, atypical CD30 + cells scattered within inflammatory cells, including lymphocytes, eosinophils, and neutrophils [27]. In LyP type B, smaller atypical cells with hyperchromatic cerebriform nuclei infiltrate the epidermis, with CD30-, CD3+, CD4 + and CD7- [28]. The immunohistochemical profile of LyP type C is very similar to type A, but contains a higher number of large atypical CD30 + cells [29]. LyP type D is a rare variant marked by pagetoid infiltration of atypical CD8 + and CD30 + epidermal cells [28]. These cells commonly express granzyme B, perforin, and TIA-1. LyP type E is defined by angioinvasive and angiodestructive features, with a dense infiltration of large CD30 + cells surrounding and invading blood vessels [30]. This subtype can present necrotic or ulcerative lesions with a more aggressive clinical progression. The sixth type of LyP is identified by *DUSP22* rearrangement, which plays a critical role in its classification. This type exhibits a biphasic morphology, showing two distinct cellular components [26].

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

SPTCL presents with isolated or multiple subcutaneous nodules and/or plaques on the limbs and trunk, often accompanied by fever and cytopenias [31]. In a study involving 95 SPTCL patients from the Northwestern University Cutaneous Lymphoma Research Centers, the majority patients had multiple tender, deep nodules, predominantly on the legs (68%), without ulceration [31]. Hepatomegaly and/or splenomegaly occurred in 15%, and palpable adenopathy in 14% [31].

Neoplastic cells exhibit positivity for CD, granzyme B, TIA-1, and perforin. Additionally, these cells are positive for βF1 and negative for CD56, CD30, and EBV [32]. While SPTCL generally has a more indolent prognosis compared to cutaneous gamma-delta T-cell lymphoma, which shares significant clinical and histopathologic overlap with SPTCL, vigilant monitoring of patients remains essential. This is particularly crucial due to the potential development of hemophagocytic lymphohistiocytosis (HLH), which has been reported in 7–45% of cases across various studies, as it can markedly worsen the prognosis [33].

Extranodal NK/T-cell lymphoma, nasal type (ENKTL)

ENKTL primarily involves the skin of the trunk and limbs, presenting as erythema, nodules, and ulcerative plaques or tumors. Micromorphologically, it is characterized by infiltration and destruction of blood vessels with CD4, CD56, and EBER expression [34]. Patients with lesions confined to the skin or with CD30 positivity have a better prognosis. Typical immunophenotypes of ENKTL tumor cells are CD3+, CD56+, granzyme B+, TIA-1 and EBER+ [4].

Chronic active EBV infection (CAEBV)

CAEBV is marked by a persistent syndrome resembling infectious mononucleosis, along with the presence of EBV viremia [35]. Although initially considered as a childhood disease, CAEBV is now recognized to occur in adults as well [36]. It predominantly occurs in East Asia, Mexico and sometimes in Western nations. A positive association between CAEBV and the human leukocyte antigen (HLA) A26 is indicated, which is often observed in East Asian populations [37]. Cutaneous manifestations of CAEBV include hydroa vacciniforme-like lymphoproliferative disorder (HV-like LPD) and hypersensitivity reactions to mosquito bites, potential to systemic EBV+T- or NK-cell lymphoma [38]. Antiviral treatments, such as ganciclovir, may be combined with corticosteroids or IVIG, which are often temporarily effective. Hematopoietic stem cell transplantation (HSCT) represents the current leading treatment choice, offering the potential for long-term remission or cure [36].

Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL)

PCGDTCL is a rare and aggressive subtype of CTCL, accounting for less than 1% of all PCLs [39]. It usually affects patients over 50 years old, with a median age range of 50 to 60 [40]. Clinically, deep plaques are the most common manifestation, though nodules, superficial plaques, and patches can also occur. Ulceration is observed in up to 50% cases [40]. Histologically, PCGDTCL is characterized by the presence of medium to large activated γδ T-cells with a cytotoxic phenotype [41]. Although most CTCLs originate from αβ T cells, PCGDTLs typically originate from γδ T cells. CD3 is expressed in nearly all cases, along with CD2, CD5, CD7, and CD56. Additionally, cytotoxic proteins like granzyme B and TIA-1 are frequently expressed, with TIA-1 being present in over 90% cases [40]. In some cases, CD30 expression has been identified [42]. The prognosis tends to be unfavorable, with a high incidence of relapse and resistance to conventional therapies.

Primary cutaneous CD8-positive aggressive-epidermotropic cytotoxic T cell lymphoma (PCAECTCL)

PCAECTCL represents a distinctive and extremely aggressive variant of CTCL, marked by the clonal expansion of CD8+cytotoxic T cells [43]. PCAECTCL presents as swiftly progressing nodules, tumors, or annular hyperkeratotic plaques, often accompanied by early ulceration or necrosis [44]. Oral mucosa and genital skin may be affected, although it is common to spread to lungs, adrenal glands, and central nervous system, lymph node and bone marrow involvement is rare [45]. The overall prognosis tends to be unfavorable, with a 5-year OS rate between 18% and 32% [44]. Histopathologically, PCAECTCL is marked by pronounced epidermotropism, especially in the basal cell layer, with atypical lymphocyte infiltration to dermis, usually extending to subcutaneous fat [46]. The atypical lymphocytes express cytotoxic markers, including granzyme B, perforin, and TIA-1, while EBV and CD56 are negative [47]. It is characterized by the widespread distribution of ulcerative lesions, highly invasive behavior, and a strong tendency for systemic dissemination.

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder (CD4 + SMTCLPD)

CD4 + SMTCLPD is an uncommon and indolent subtype of CTCL [48]. It often manifests as solitary or localized lesions as papules, plaques or nodules, which are predominantly on the head, neck, and upper trunk [48]. Systemic involvement is extremely rare. The prognosis is favorable, with an exceptionally high ORR of 100% [49]. However, recurrence on the face may pose therapeutic challenges. Histologically, CD4 + SMTCLPD is characterized by nodular or diffuse infiltration of small to medium-sized CD4 + T-cells in the dermis and subcutaneous tissue, without significant epidermotropism [50]. The tumor cells express CD3 and CD4, while CD8, CD30 and cytotoxic markers are notably negative, distinguishing CD4 + SMTCLPD from other cutaneous lymphoproliferative disorders [51].

Primary cutaneous acral CD8 + T-cell lymphoma (Acral CD8 + TCL)

Acral CD8 + TCL is identified by diffuse infiltration of medium-sized CD8 + cytotoxic T-cells [52], which presents as solitary and slow-growing papules or nodules on acral sites such as the ears, nose, and feet [53]. T-cells is characterized by positivity for CD3 and CD8, absence of CD4 and CD30. Additionally, there is variability in the the loss of pan-T-cell antigens, including CD2, CD5, and CD7 [51]. These cells also show positivity for TIA-1, but negative for cytotoxic proteins granzyme B and perforin [51]. In comparison to other CD8 + T-cell lymphomas, this subtype is known for its indolent process with a more favorable outcome. Local excision or radiotherapy have proven to be effective management strategies.

Primary cutaneous peripheral T-cell lymphoma, not otherwise-specified (PCTCL-NOS)

PCTCL-NOS does not fit into any well-defined CTCL category [54], which appears as violaceous plaques or nodules and can involve various skin regions. Some of the cells are positive for CD4 and may also display markers indicative of T-follicular helper cell differentiation, which can lead to diagnostic confusion with CD4 + SMTCLPD [26]. The prognosis for PCTCL-NOS is typically poor, primarily because of its high tendency for systemic dissemination. The 5-year OS rate is estimated to be only 20–30% [55]. Treatment usually involves multi-agent chemotherapy, and in some cases, HSCT is considered. Given the aggressive nature and variable clinical presentation of PCTCL-NOS, early and accurate diagnosis is crucial for effective management.

CBCL

About a quarter of all cutaneous lymphomas are B-cell-based and can be classified into three major subgroups. The first subgroup is primary cutaneous follicle center lymphoma (PCFCL), an indolent B-cell lymphoma. The second subgroup is primary cutaneous marginal zone lymphoma (PCMZL), a low-grade B-cell lymphoma consisting of small B-cells, lymphoplasmacytoid cells, and plasma cells. The third subgroup is primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT) [56]. Additionally, two rare subtypes are recognized: EBV-positive mucocutaneous ulcer (EBVMCU) and intravascular large B-cell lymphoma (IVLBCL) [4]. However, IVLBCL typically presents with widespread extracutaneous involvement at diagnosis, so IVLBCL is categorized as a systemic lymphoma but not CBCL [57]. EBVMCU is a newly identified EBV-associated lymphoproliferative disorder that primarily affects the skin and mucosa.

PCFCL

PCFCL typically presents as isolated or localized lesions on the scalp, head, neck, or trunk [3]. The neoplastic cells show expression of B-cell-related antigens, specifically CD20 and CD79a, with consistent expression of bcl-6 [58]. Additionally, in PCFCL, bcl-2 staining is faint and detected in a few neoplastic cells, further distinguishing it from other forms of follicular lymphoma [59].

PCMZL

PCMZL usually manifests as solitary or multiple papules, nodules, or plaques on the limbs and trunk [60–61]. These B cells are characterized by their irregular and inconspicuous nucleoli, along with abundant pale cytoplasm [62]. Marginal zone B cells express CD20, CD79a, and bcl-2, while CD5, CD10, and bcl-6 are negative [59]. Additionally, plasma cells express CD138 and CD79a, while notably lacking CD20 expression [63].

PCDLBCL, LT

PCDLBCL, LT typically presents in elderly individuals (over 70 years old) who develop soft pink to purplish nodules and masses, often on one or both lower limbs [61]. There is a paucity of small B cells and relatively few reactive T cells, which are usually confined to the periphery of blood vessels [16]. Expression of bcl-2, IRF4/MUM-1, and bcl-6 is high while CD10 expression is typically negative [4].

Treatment for CTCL

SDT for early-stage CTCL

The majority of CTCL patients present with early-stage disease (stages IA–IIA), typically characterized by patches or plaques localized to the skin. Treatment strategies for early-stage CTCL primarily focus on SDT [64]. Common options include 0.02% mechlorethamine gel, bexarotene, imiquimod, phototherapy, and radiation therapy (Table 2).

0.02% mechlorethamine gel

Mechlorethamine, also known as chlormethine or nitrogen mustard, is an alkylating agent that effectively treats MF by inhibiting tumor cell proliferation and disrupting interactions among keratinocytes, Langerhans cells, and T cells [65]. Early formulations were mostly solutions or ointments, but the newer gel formulation shows improved efficacy and a faster, higher response rate compared to traditional ointments [66]. A multicenter, randomized study involving 260 patients with stage IA to IIA MF compared 0.02% mechlorethamine gel to 0.02% mechlorethamine ointment, showing response rates of 59% and 48%, respectively [67]. No serious drug-related adverse reactions were observed, with the most common toxicities being irritant contact dermatitis, allergic reactions, and pigmentation [67].

Bexarotene

Bexarotene, a third-generation synthetic retinoid with high affinity for the retinoid X receptor (RXR), regulates gene transcription related to cell differentiation and apoptosis, thereby inhibiting tumor cell growth. It is approved in the USA and Europe for advanced MF/SS [68]. In a phase I/II open -label, dose-escalation trial involving 67 adults with IA-IIA MF, the ORR was 63%, with higher efficacy in previously untreated patients (75%) compared to those who had received prior treatments (67%) [69].

Small-molecule agonists at TLR7 and TLR8

Imiquimod is a Toll-like receptor agonist that binds to TLR7 on macrophages, monocytes, and dendritic cells (DCs), inducing the release of IFN-a, IL-6, and IL-12, and converting the Th2 cytokine spectrum to Th1 [70]. Due to Th2 cytokines in MF progression, imiquimod shows promise in treating MF [71, 72]. One case report described a patient achieving CR after two months of imiquimod treatment despite ineffective local steroid therapy [73].

Resiquimod, an imidazoquinoline and agonist for TLR7 and TLR8, induces more substantial cytokine secretion and cellular immunity than imiquimod. Resiquimod activates the TLR signaling pathway, which in turn activates NF-kB along with other transcription factors, resulting in enhancing Th1 immune responses [73]. Furthermore, resiquimod seems to activate epidermal Langerhans cells, resulting in increased T-lymphocytes activation [73]. A phase 1 study in 12 CTCL patients with stage IA-IIA, resiquimod gel showed significant improvement in treated lesions, and 30% achieved complete remission (CR). Remarkably, resiquimod also caused regression in untreated lesions, indicating its potential as a skin -targeting compound [74].

Phototherapy

Phototherapy, including psoralen, ultraviolet A radiation (PUVA) and narrowband ultraviolet B (NBUVB), is the primary treatment option for MF stages IA, IB, and IIB [75]. A meta-analysis of IA-IIA MF showed similar response rates with NBUVB and PUVA [76]. NBUVB is suitable for plaque, while PUVA may be more appropriate for patients with thicker plaques or intolerant to PUVB treatment due to deeper dermal penetration [77]. However, 30% of MF patients show insufficient response to PUVA and require new treatment options. Combination therapy included retinoids and interferon-alpha can enhance efficacy, reduce the cumulative PUVA dose, and minimize related adverse reactions. Additionally, small-molecule inhibitors of ataxia telangiectasia and Rad3 -related kinase (ATR) have been reported to enhance lymphoma cell sensitivity to PUVA and induce tumor cell apoptosis [78].

Radiation therapy

Radiation therapy, including local superficial radiation and total skin electron beam therapy (TSEBT), remains one of the most effective treatments for CTCL. TSEBT, in particular, delivers ionizing radiation across the entire skin surface, offering deeper penetration than nitrogen mustard and phototherapy [79]. Malignant T cells are highly sensitive to radiation, making TSEBT effective in reducing tumor load. This therapy targets lymphomas by precisely delivering radiation doses to the epidermal and dermal layers. The ORR can reach 92% with conventionally fractionated low-dose TSEBT [80]. TSEBT is recommended for patients who have failed phototherapy or a first-line treatment for those with extensive skin involvement [81].

Systemic therapies for advanced-stage CTCL

In advanced-stage CTCL, skin-directed therapies are less effective, and systemic treatments become necessary. Recent advances in monoclonal antibodies, small molecule

Table 2 Currently available therapies for PCLs

Author	Therapy	Target	Disease	Efficacy
Lessin et al.	0.02% Mechlorethamine Gel	-	IA- IIA MF/CTCL	ORR was 59%
Breneman et al.	Bexarotene	RXR	IA- IIA MF	ORR was 63%
Shalabi et al.	Imiquimod	TLR7	FMF	A case achieved CR
Rook et al.	Resiquimod	TLR7, TLR8	IA- IIA CTCL	CR was 30%
Phan et al.	Phototherapy	-	IA- IIA MF	PUVA: CR was 73.8% NBUVB: CR was 62.2%
Elsayad et al.	Radiation therapy	-	MF/SS	ORR was 92%
Miljkovic et al.	Alemtuzumab	CD52	ATL	ORR was 45%
Prince et al.	Brentuximab Vedotin (BV)	CD30	CD30+MF or PCALCL	ORR4 was 56.3%
Kim et al.	Mogamulizumab	CCR4	R/R MF or SS	ORR was 28%
Bagot et al.	Lacutamab	KIR3DL2/CD158k	R/R CTCL	ORR was 36%
Leupin et al.	Cusatuzumab	CD70	R/R CTCL	ORR was 23%
Olsen et al.	Vorinostat	HDAC	IB- IVA MF/SS	ORR was 29.7%
Horwitz et al.	Duvelisib	PI3K-δ and PI3K-γ	R/R CTCL	ORR was 31.6%
Moskowitz et al.	Ruxolitinib	JAK1 and JAK 2	R/R PTCL or MF	Cohorts 1: CBR was 53%
Kawai et al.	E7777	IL-2R	R/R CTCL	ORR was 31%
Khodadoust et al.	Pembrolizumab	PD-1	MF/SS	ORR was 38%
Weichenthal et al.	Oral bexarotene	RXR	MF	ORR was 37%
Kuzel et al.	Recombinant IFN-α2a+PUVA	-	CTCL	ORR was 93%
Hansen et al.	PegIFN-α2a	-	MF/SS	ORR was 55.2%
Zackheim et al.	Methotrexate	-	MF	ORR was 33%
Horwitz et al.	pralatrexate	-	MF/SS or PCALCL	ORR was 45%
Haverkos et al.	Nivolumab+DA-EPOCH	PD-1	SPTCL/PTCL	EOT ORR was 89%
Rupoli et al.	Bexarotene+PUVA	-	R/R MF/SS	ORR was 85.6%
Horwitz et al.	BV+CHP	CD30	CD30+PTCL	PFS was 48.2 months
Vu et al.	Romidepsin+liposomal doxorubicin	HDAC	CTCL	ORR was 70%
Iyer et al.	Pembrolizumab+romidepsin	PD-1+HDAC	R/R PTCL	ORR was 44%
Senff et al.	Rituximab+CHOP	CD20	PCDLCBCL, LT	ORR was 81%
Di Raimondo et al.	Rituximab+lenalidomide+pembrolizumab	CD20、PD-1	PCDLCBCL, LT	A case achieved CR
Fox et al.	Ibrutinib	BTK	PCDLBCL-LT	A patient achieved complete resolution of the skin disease
Beylot-Barry et al.	Lenalidomide	-	R/R PCDLBCL-LT	ORR was 26.3%
Walter et al.	Venetoclax	BCL2	PCDLBCL-LT	A case achieved CR

ORR: overall response rate; CR: complete response; PFS: progression-free survival; CBR: clinical benefit rate

inhibitors, immunotherapy, and combination treatment strategies are transforming the CTCL treatment landscape (Table 2).

Monoclonal antibodies

Alemtuzumab

CD52 is a glycoprotein composed of 12 amino acid residues and anchored to glycosylphosphatidylinositol. This molecule is prominently expressed on the surface of immune cells and most B and T cell malignancies, but is absent in hematopoietic progenitors, erythrocytes, and platelets [82]. Alemtuzumab, a humanized monoclonal antibody targeting CD52, functions by depleting T and B lymphocytes through mechanisms such as ADCC and CDC. A phase I trial evaluated the safety and efficacy of recombinant human IL-15 in combination with standard intravenous alemtuzumab therapy in ATL with ORR 45% [83], providing a scientific basis for further investigation of IL-15 combined with alemtuzumab in ATL [83]. However, due to CD52 expression on all immune cells, the use of alemtuzumab can lead to widespread immune suppression, thereby potentially limiting its clinical benefits [84].

Brentuximab Vedotin (BV)

CD30, also known as TNFRSF8 or Ki-1, is a glycoprotein receptor belongs to the tumor necrosis factor receptor (TNFR) family. This receptor is predominantly expressed

in various types of lymphomas, including classical Hodgkin lymphoma (HL), LyP, and PCALCL [85]. While CD30 expression in MF is heterogeneous, it plays a significant role in immune responses, supporting T-cell survival, and balancing Th1 and Th2 immune responses, particularly in autoimmune and inflammatory conditions. BV is an antibody drug conjugate (ADC) composed of a chimeric IgG1 antibody that specifically targets CD30, combined with the cytotoxic drug monomethyl auristatin E (MMAE) [85], which disrupts microtubule structure, inhibits polymerization and induces programmed cell death upon binding to CD30 [86].

BV is approved for CD30+lymphoproliferative disorders, such as PCALCL and MF. In a phase III randomized multicenter trial, 128 previously treated patients with CD30+MF or PCALCL were enrolled. BV showed a notable improvement in median progression-free survival (PFS), compared to conventional therapy. The ORR in the BV group was 56.3% [87]. A randomized trial comparing BV as second-line treatment with other standard therapies in patients with CD30+MF or PCALCL who had previously received systemic therapy revealed that the median treatment duration for BV was 8.4 months, significantly longer than the 5.2 months observed with other standard treatments. Furthermore, the ORR for BV was notably high at 82.1%, compared to 66.5% for alternative therapies. These findings underscore the favorable clinical outcomes associated with BV, suggesting that it may be the preferred treatment option for patients with CD30+CTCL [88].

Mogamulizumab (MOG)

MOG is an innovative monoclonal antibody designed to target the C-C chemokine receptor 4 (CCR4), leading to target cell depletion. It has been approved by the Food and Drug Administration (FDA) *t*o treat trecurrent and refractory (R/R) peripheral T-cell lymphoma (PTCL) and CTCL. MAVORIC trial extended its application to R/R MF/SS [89]. However, novel CCR4 mutations affecting the N-terminus and transmembrane domains may develop resistance to treatment, resulting in disease progression [89, 90].

In a phase 3 international open-label randomized controlled trial, 372 patients with R/R MF or SS, who had failed≥1 systemic therapy, were enrolled across 61 medical centers. Patients were randomized to receive either MOG or vorinostat. MOG resulted in longer PFS compared to vorinostat, with a median of 7.7 months versus 3.1 months [91]. The ORR was 28% in MOG group, compared to 5% in vorinostat group. The most common serious adverse events with MOG included pyrexia and cellulitis, while cellulitis, pulmonary embolism and sepsis in vorinostat group [91].

Lacutamab

KIR3DL2, referred to as CD158k, is part of the killer cell immunoglobulin-like receptor (KIR) family and is predominantly found in CTCL, especially in SS [92]. Lacutamab (IPH4102), a humanized monoclonal antibody targeting KIR3DL2, promotes the apoptosis of KIR3DL2+cells through ADCC and phagocytosis [92]. In an international phase 1 clinical trial, 44 patients with R/R CTCL were treated with Lacutamab, which was administered via intravenous infusion [93]. After a 14-month follow-up, the ORR was 36%, with the duration of response (DOR) averaging 13.8 months. Among the adverse reactions, peripheral edema was reported in 27% of patients, and fatigue affected 20%. Lymphopenia emerged as the most prevalent grade 3 adverse event [93].

Cusatuzumab

CD70 is intermittently expressed by mature DCs and highly activated T-cells and B-cells, but it is constitutively expressed in solid and hematological cancers with poor prognosis. Upon binding to CD27, NF-kB and c-Jun kinase pathways are activated, promoting tumor cell proliferation, survival, and immune evasion by recruiting or sustaining regulatory T cells [94]. Cusatuzumab is a high-affinity CD70 monoclonal antibody that inhibits leukemia stem cell proliferation by blocking CD70-CD27 signaling and induces cell death in CD70-positive cancer cells through CDC and ADCC mechanisms [18]. In a phase I/II cohort study involving 27 patients with relapsed/refractory (R/R) CTCL, cusatuzumab demonstrated an ORR of 23% and 5 mg/kg appears to be the optimal dosage [95].

Small molecule inhibitors

Histone deacetylase inhibitors (HDACi)

HDACi inhibit HDAC activity and regulate histone acetylation, exerting anti-tumor effects [96]. Vorinostat and romidepsin have shown promising applications in various cancers, approved to treat R/R CTCL [97, 98]. In MF, vorinostat exhibits anti-tumor properties by disrupting T cell receptor signaling, inhibiting the MAPK pathway, and downregulating anti-apoptotic genes such as CTLA-4, CXCR4, and CCR7 [99]. A phase IIb multicenter study of vorinostat in patients with MF/SS showed an ORR of 29.7% [100]. Resminostat is an HDAC inhibitor targeting HDAC classes I, IIb, and IV. Karagianni et al. reported that resminostat combined with JAK inhibitor ruxolitinib exhibited cytotoxic effects in CTCL cells, indicating a potentially

effective therapeutic approach for CTCL [101, 102]. Resminostat is currently being evaluated in the pivotal European RESMAIN study, which aims to assess its role in maintenance therapy for advanced MF/SS patients [102].

PI3K/AKT inhibitors

PI3K is a lipid kinase crucial in intracellular signal transduction, consisting of four human subunits (α, β, δ, and γ) [103]. PI3K inhibitors have demonstrated efficacy in B-cell malignancies [103]. Key proteins such as Akt, mTOR, and p70S6K in the PI3K/Akt pathway are implicated in MF progression, making pathway inhibition a novel therapeutic strategy under investigation in CTCL clinical trials [86]. Duvelisib (IPI-145), an oral inhibitor of PI3K-δ and PI3K-γ, was evaluated in a phase 1 open-label study for R/R CTCL with an ORR of 31.6%, indicating notable efficacy in R/R CTCL [104]. However, the safety of duvelisib must be considered. The most common side effects included elevated transaminases, neutropenia and maculopapular rash [104]. Tenalisib (RP6530) is a novel inhibitor targeting PI3K δ/γ, which showed promising results in a Phase I/Ib clinical study [105]. Overall, PI3K inhibitors exhibit favorable clinical activity in the treatment of R/R CTCL.

JAK-STAT inhibitors

The JAK-STAT pathway plays a pivotal role in promoting PC-TCL progression, with somatic mutations in JAK1 and JAK3 leading to dysregulated signaling in PC-TCL [106]. Ruxolitinib, a JAK1 and 2 inhibitors, administered at 20 mg PO twice daily in patients with R/R PTCL or MF. Among MF patients, one achieved a durable partial response lasting over 18 months. Cohorts 1, 2, and 3 of PTCL cases showed clinical benefit rates (CBRs) of 53%, 45%, and 13%, respectively [107].

Immune checkpoint inhibitors

Immune checkpoint molecules, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), inhibit T-cell responses and allow tumors to evade immune surveillance [108]. PD-1 or PD-L1 inhibitors can activate CD8+cytotoxic lymphocytes, enhancing anti-tumor immunity, offering a promising strategy to overcome tumor-induced immunosuppression and improve T-cell-mediated responses in CTCL treatment [109]. A multicenter phase II trial involving 24 patients with advanced-stage MF/SS received pembrolizumab at a dose of 2 mg/kg every three weeks, up to 24 months, with an ORR of 38% [110]. Haverkos et al. reported improved outcomes with the combination of nivolumab and DA-EPOCH chemotherapy as the first-line treatment for PTCL, including CTCL, resulting in higher CR rates and extended EFS [111].

CD47 is an immune checkpoint protein that interacts with signal regulatory protein alpha (SIRPα) to prevent macrophage-mediated phagocytosis [112]. This protein is highly expressed on Sézary cells [113]. TTI-621, an immune checkpoint inhibitor, designed to disrupt the binding between CD47 on tumor cells with SIRPα on macrophages, potentially enhancing anti-tumor immunity [112]. Multiple clinical trials have shown that targeting CD47 is a promising treatment option for CTCL [113, 114].

Immunotoxin

Denileukin diftitox is a recombinant fusion protein that combines the full -length sequence of human IL-2 with modified cytotoxic and membrane-translocating domains from diphtheria toxin. It targets the IL-2 receptor on malignant T cells, leading to internalization and subsequent polypeptide chain formation, which disrupts protein synthesis and induces cell death [115]. Despite FDA approval, denileukin diftitox was withdrawn from the market in 2014 due to production issues related to E. coli expression and purification [116]. E7777, an improved formulation of Denileukin diftitox containing diphtheria toxin fragments A and B with human IL-2, was approved in Japan in 2021 for treating R/R CTCL [116]. In a pivotal multicenter phase II trial involving 37 patients, the ORR in CTCL patients was 31%, with a median PFS of 4.2 months [117]. Common adverse reactions included elevated ALT/AST, hypoalbuminemia, and capillary leak syndrome [117]. Wang et al. developed a human IL2 fusion toxin and an anti-human CCR4 immunotoxin (CCR4 IT) to target CD25+CCR4+CTCL, with CCR4 IT proven to be more effective than IL-2 fusion toxin [118]. The team also developed IL2-CCR4 bispecific IT, which which is more effective than IL2 fusion toxin or CCR4 IT alone, representing a promising approach for treating R/R CD25+and/or CCR4+CTLC [118].

MicroRNAs

MicroRNAs are small noncoding RNAs regulating protein expression post-transcriptionally in normal and pathological cells [119]. MicroRNA expression profiles have been investigated for diagnosing and managing MF/SS, identifying specific miRNAs like miR-155, miR-21, and miR-199/214 up-regulated in MF, distinguishing it from benign diseases with high specificity and sensitivity [119, 120]. MiR-155, associated with poor lymphoma prognosis, plays a role in MF progression. Cobomarsen is a synthetic miR-155 locked oligonucleotide inhibitor that downregulates cell

survival related gene pathways, inhibits tumor proliferation in CTCL, and induces apoptosis [121].

CAR-T therapy

CAR-T therapy is a potential option for CTCL. The most promising target for CAR-T in CTCL, particularly in PCALCL and CD30-positive MF, is CD30 [122]. CD4, a common marker in MF and SS, also presents a therapeutic opportunity, although it carries the risk of depleting normal CD4 + helper T-cells, leading to severe immunosuppression [123]. CD7, another emerging target in CTCL, is expressed on malignant T-cells in both MF and SS [123]. While clinical trials using CD30-targeted CAR-T cells have shown encouraging results in refractory CD30 + lymphomas, no trials have yet been conducted specifically for CTCL [85]. A major challenge in applying CAR-T therapy to CTCL is the lack of specific antigens unique to malignant T-cells. Many of the target antigens, such as CD3, CD5, and CD7, are also expressed on healthy T-cells, leading to the risk of depleting normal T-cells and increasing susceptibility to infections [124]. Overcoming these challenges will be key to expanding the use of CAR-T therapy in CTCL.

Other medications

Oral bexarotene has demonstrated efficacy in treating relapsed/refractory CTCL. The ORR differed among CTCL subtypes, with 37% for MF, 50% for CD30 + pcALCL, 60% for LyP, and 33% for both SS and other rare forms of CTCL. The treatment was well tolerated, with the most common side effects being hypothyroidism and hyperlipidemia [125].

IFN-α is an immunomodulatory agent that enhances immune responses by stimulating cytokine production and T-cell activation. It has been used as first-line and adjuvant therapy for early- and advanced-stage CTCL. IFN-α treatment results in an ORR of approximately 25–30% when used as monotherapy. Its efficacy is often enhanced when combined with other therapies, such as phototherapy (e.g., PUVA). Combining IFN-α2a with PUVA results in an impressive ORR of 93% [126]. A multicenter study involving pegIFN-α2a reported an ORR of 55.2%, with 68.6% of patients experiencing adverse events such as fatigue and blood count abnormalities [127].

Methotrexate (MTX) is an antimetabolite and folate antagonist widely used for advanced-stage CTCL. The ORR of low-dose MTX (median dose: 25 mg/week) is 33–58% [128]. Pralatrexate is a potent antifolate chemotherapy agent that has shown significant promise in the treatment of R/R CTCL. It inhibits folate metabolism, thereby interfering with DNA synthesis and cell proliferation, with an ORR of 52% and a DOR of 8.7 months [129]. In a group of 29 patients with refractory MF/SS and PCALCL, low-dose pralatrexate achieved an ORR of 45% after 4 cycles [130].

Combination therapies

In a prospective phase II trial evaluating low-dose bexarotene combined with PUVA for refractory and/or resistant MF/SS, the ORR was 85.6% after induction therapy and 76.2% at the end of maintenance therapy [131]. Combination maintenance therapy of gemcitabine and besarotene help to control plaques and plaques associated with MF [132]. Systemic treatments like BV are commonly combined with chemotherapy or radiotherapy to achieve better disease control. Oymanns M et al. reported that in patients with stage IIB MF, combination of BV and low-dose electron beam therapy led to CR in some patients [133]. A phase III randomized controlled trial, ECHELON-2, demonstrated that the combination of BV with cyclophosphamide, doxorubicin, and prednisone (BV + CHP) was more effective than CHOP in patients with CD30 + PTCL, achieving a PFS of 48.2 months [134]. In a phase I clinical trial involving 23 patients (11 with CTCL and 12 with PTCL), romidepsin combined with liposomal doxorubicin yielded an ORR of 70% in CTCL [135]. Combination of pembrolizumab and romidepsin for R/R PTCL achieved an ORR of 44%, with a CR rate of 20% [136]. These results highlight the potential advantages of combination therapies.

Treatment for CBCL

Treatment strategies for CBCL are determined by the patient's symptoms, disease subtype, stage, and the number of lesions. For indolent CBCL, local therapies including surgery, radiotherapy, or intralesional corticosteroids are suitable. For aggressive subtypes or spread disease, CHOP-like regimens combined with rituximab are recommended. However, for relapsed or resistant patients, there is a pressing need for innovative systemic treatment approaches (Table 2).

Monoclonal antibodies

CD20 is a B-cell specific antigen expressed at all stages of B cells except early progenitors and late plasma cells [137]. Rituximab and ofatumumab are the two most commonly used type I anti-CD20 antibodies for CBCL. Rituximab with CHOP is considered as first-line therapy, which induces cell death through ADCC, CDC, and direct induction of apoptosis [138, 139]. Rituximab is often administered as monotherapy for PCMZL and PCFCL, showing high response rates and durable remissions [140]. For aggressive subtypes

such as PCDLBCL-LT, rituximab is typically combined with CHOP to enhance therapeutic outcomes [140, 141]. However, approximately 52% patients experience relapse after the initial treatment [142]. In R/R cases, rituximab can also be combined with other systemic therapies such lenalidomide and pembrolizumab [143]. Additionally, radioimmunotherapy (RIT) is a growing area of research aimed at enhancing the effectiveness of monoclonal antibody therapies. Two anti-CD20 IgG radioconjugates, Y-ibritumab and I-tositumomab, have received FDA approval to treat NHL and could potentially be used for PCDLBCL-LT in the future [140].

Small molecule inhibitors

MYD88 L265P mutations are prevalent in PCDLBCL-LT patients, indicating poor prognosis, which can be inhibited by Bruton's tyrosine kinase (BTK) inhibitors [144]. Ibrutinib, a BTK inhibitor, has shown efficacy in treating PCDLBCL-LT [144]. Combination of ibrutinib with rituximab and lenalidomide represents a novel therapeutic approach in PCDLBCL-LT [145].

Lenalidomide, an immunomodulatory drug, boosts T-cell and NK cell activity and inhibits angiogenesis by downregulating key factors like VEGF and FGF. Moreover, lenalidomide disrupts pro-survival pathways, such as NF-κB, and induces apoptosis, leading to the direct elimination of cancerous cells [146]. A multicenter phase II trial assessed the safety and efficacy of lenalidomide in refractory/relapsed PCDLBCL-LT revealed an ORR of 26.3% [147].

Venetoclax, a selective BCL2 inhibitor, has shown clinical efficacy in chronic lymphocytic leukemia (CLL) [148–149]. A case report by Walter highlighted the successful application of venetoclax as a monotherapy in a patient with PCDLBCL-LT, leading to CR, however the disease relapsed quickly after discontinuation [150]. This outcome suggests that combination therapies may be needed to achieve durable responses [150].

CAR T therapy

CAR T therapy targeting CD19 has gained FDA approval for R/R DLBCL [151]. Combination therapies incorporated CAR-T with cytokines or immune checkpoint inhibitors are currently under investigation to assess their potential to enhance the effectiveness for lymphoma treatment [3]. These approaches may hold substantial value for the future management of PDLCBL, LT.

Conclusion

Although early PCLs patients typically achieve good treatment outcomes, late stage patients often face a severe prognosis characterized by poor treatment response, frequent recurrence, and low sustained remission rates. Due to the diverse genetic profiles and clinical presentations, it's imperative to tailor personalized treatment plans for each individual. Novel drugs with substantial therapeutic benefits and minimal toxicity are expected to significantly enhance patient outcomes.

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Data availability The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was subject to approval by the Research Ethics Committee of Tianjin Medical University Cancer Institute and Hospital.

Consent for publication Not applicable.

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