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Primary cutaneous lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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introduction

Cutaneous lymphomas (CL) are the second most common extranodal non-Hodgkin's lymphomas. Their incidence is estimated at 1/100 000 yearly. Primary CL develop by definition in the skin and remain confined to the skin for a long period of time, while secondary CL reflect cutaneous spread from disseminated primary nodal or extranodal lymphomas. Primary CL include a wide spectrum of clinically and histologically heterogeneous lymphoproliferative neoplasms: 75% of CL are cutaneous T-cell lymphomas (CTCL); 25% cutaneous B-cell lymphomas (CBCL); and a few percent other uncommon forms. CL and nodal or extracutaneous lymphomas with the same cytomorphology may differ greatly in regard to clinical features, therapy and prognosis (Table 1).

diagnosis

The diagnosis of CL requires extensive clinical experience and relies upon a detailed history, clinical observation, histologic analysis (including the appropriate immunohistochemical studies based on the working diagnosis) and proof of clonality in lesional skin [suspected Sezary syndrome (SS): in the peripheral blood]. Other extranodal manifestations should be also excluded. However, many inflammatory skin diseases may reveal clonality, as detected by PCR.

staging

Recently, the ISCL and EORTC published a new TNM staging system for MF/SS. This classification is less helpful for CTLC other than mycosis fungoides (MF)/SS.

therapy

Especially MF/SS are indolent neoplasms with a very wide variation in clinical presentation. In the early stages, they affect the quality of life due to their impact on skin appearance and annoying symptoms such as pruritus. In some cases they can already be disfiguring in early disease stages. In advanced stages, local skin problems are accompanied by systemic immune suppression which results in an increased risk of infections and secondary malignancies. Some of the late-stage problems in MF/SS patients might have been aggravated by earlier therapeutic interventions, e.g. radiotherapy or phototherapy may contribute to mutations that increase the proliferative and invasive capacity of the tumor cell populations. Cytotoxic drugs favor infectious complications. Most patients with advanced disease may die due to secondary problems such as infections.

MF/SS patients are mostly of advanced age and have many concomitant diseases Thus, a realistic goal for CL treatment is to achieve long-lasting remissions in a significant percentage of patients with drugs that can be safely used without long-term toxicity. Initial therapy should be skin directed. If the disease is not sufficiently controlled, systemic biological therapy can be added. Aggressive polychemotherapy is only justified for advanced disease.

therapy of CTCL: mycosis fungoides, follicular mucinosis and pagetoid reticulosis

A stage-adjusted, conservative therapeutic approach is recommended for MF and its variants. In earlier stages, topical treatments should be favored such as topical corticosteroids, PUVA (psoralen plus UVA), topical cytostatic agents such as mechlorethamine (HN2) and BCNU or radiation therapy with electron beam or soft X-rays.

In advanced stages, the addition of total skin electron beam therapy (TSEBT) (30 Gy) combined with chemotherapy with various topical treatments [phototherapy and mechlorethamine (nitrogen mustard)] has resulted in a higher response rate. However, there were serious side-effects and no difference in overall survival rate was observed.

In more advanced stages, combined topical and systemic therapy is often employed; e.g. PUVA combined with systemic retinoids or recombinant interferon-α (IFN-α).

Localized forms of MF such as pagetoid reticulosis are best treated with radiation therapy—soft X-rays (12–20 Gy total dose 2 Gy 2 $\times$ weekly for 3–5 weeks) or electron beam (30–40 Gy) (Table 2).

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Table 1. Cutaneous T-cell, B-cell and NK-cell lymphomas: clinic, phenotype and genotype

Diagnosis	Clinical features	Immune phenotype
Mycosis fungoides variants and subtypes	Patches and plaques, later tumors	CD3+, CD4+, CD45R0+, CD8– rarely, CD4–, CD8+
Folliculotropic MF	Follicular mucinosis, alopecia	
Pagetoid reticulosis	Solitary, often hyperkeratotic, patch or plaque	
Granulomatous slack skin	Circumscribed areas of initially, diffusely infiltrated, later on slack skin, typically in groins and axillae.	
Sézary syndrome	Erythroderma; hyperkeratosis of palms and soles, lymphadenopathy, alopecia.	CD3+, CD4+, CD45R0+, CD8–
Primary cutaneous CD30-positive lymphoproliferative disorders		CD3+ or CD3–, CD4+, CD30+, frequent expression of cytotoxic proteins, CD8+ cases possible.
Primary cutaneous anaplastic large cell lymphoma	Solitary to localized nodules and tumors with or without ulceration, sometimes spontaneous regressions.	
Lymphomatoid papulosis	Papular and papulonecrotic skin lesions that may ulcerate during regression, and may heal with a superficial scar.	
Subcutaneous panniculitis-like T-cell lymphoma	Solitary or multiple subcutaneous nodules to indurated plaque-like lesions	CD3+, CD4–, CD8+, cytotoxic proteins, typically TCRαβ+ (betaF1+), CD56–
Extranodal NK/T-cell lymphoma, nasal type	Mid-facial destructive tumor; multiple plaques and tumors on trunk and extremities	CD2+, CD56+, cytoplasmic CD3, cytotoxic proteins, no surface CD3; EBV !
Primary cutaneous peripheral T-cell lymphoma, unspecified		
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)	Mostly disseminated eruptive patches, plaques and nodules with erosions, ulceration and necrosis	TCRβ+, CD3+, CD8+, cytotoxic protein+, CD45RA+, CD45R0–, CD4–, CD5–, CD7+/–, EBV–
Cutaneous γ/δ T-cell lymphoma (provisional)	Dissiminated plaques and ulcero-necrotic nodules. Involvement of mucosal membranes	TCRβ–, CD3+, CD2+, CD5–, CD7+/–, CD56+, TCRδ+
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	Solitary or few plaques or tumors	CD3+, CD4+, CD8–, CD30–
Precursor hematologic neoplasm	Typically multiple nodules and tumors, often bruise like aspect	CD4+, CD56+, CD8–, CD7+/–, CD45RA+, CD123+ BDCA1+
CD4+/CD56+ hematodermic neoplasm (formerly blastic NK-cell lymphoma)		
Cutaneous B-cell lymphomas		
Primary cutaneous marginal zone B-cell lymphoma	Multiple red papules plaques or nodules	CD20+, CD79a+, BCL2+, BCL6– (marginal zone B-cells)
Primary cutaneous follicle center lymphoma	Solitary or grouped plaques and tumors	CD20+, CD79a+, BCL6+, BCL2–, CD10+/–, MUM-1–, FoxP1–
Primary cutaneous diffuse large B-cell lymphoma, leg type	Red to bluish-red tumors (legs, in elderly patients)	CD20+, CD79a+, BLC2+, BCL6+, MUM-1+, FoxP1+
Primary cutaneous intravascular large B-cell lymphoma	Net-like reddish patches and plaques	CD20+, CD79a+

TCR, T-cell receptor; Ig, Immunoglobulin gene.

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Table 2. Therapy recommendations for MF, MF variants and pagetoid reticulosis (level of evidence III)

Stage	Recommended therapy First line	Second line	Comments
IA	Watch and wait	Bexarotene gel (not available in Europe)	
	PUVA		PUVA favored in Europe; UVB/TL01 (for patches)
	Topical corticosteroids class III–IV		
	Topical HN2/BCNU		
	UVB/UVB narrow band		
Unilesional MF; pagetoid reticulosis	Radiation therapy (soft X-rays or electron beam, total dose 30–40 Gy; 2 Gy 5 × weekly)	Topical PUVA	These disorders represent special presentation forms of CTCL in Stage IA
		Intralesional IFN	
		Topical corticosteroids class III–IV	
		Bexarotene gel or PUVA + retinoids	
IB–IIA	PUVA	PUVA + IFN-α	
	Topical HN2/BCNU	Oral bexarotene	
IIB	PUVA + IFN-α and radiation therapy for tumors	Low-dose methotrexate oral bexarotene	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
	Topical HN2/BCNU	Total body electron beam	
		Denileukin diftitox	
III[a]	PUVA + IFN-α	Low-dose methotrexate	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
	Topical HN2/BCNU	Oral bexarotene	
	Extracorporeal photopheresis	Total body electron beam	
		Chlorambucil/corticosteroids	
		Vorinostat	
IVA	PUVA + IFN-α	Low-dose methotrexate	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
	Extracorporeal photopheresis	Oral bexarotene	
	Evt. combined with IFN or methotrexate	Total body electron beam	
		Chlorambucil/corticosteroids	
		Vorinostat	
		Low-dose long-distance (2 m) soft X-rays	
IVB	PUVA + IFN-α	Oral bexarotene	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
	Chlorambucil/corticosteroids	Gemcitabine	
	Liposomal doxorubicin	CHOP polychemotherapy	
	Soft X-rays or electron beam for tumors	Denileukin diftitox	
		Cladribine (2-chlorodeoxyadenosine)	
		Gemcitabine	
		Vorinostat	
		Alemtuzumab (anti-CD52)	

[a]Erythrodermic MF.

lymphomatoid papulosis and large cell C-ALCL

Primary cutaneous CD30+ lymphoproliferative disorders have an excellent prognosis. Both lymphomatoid papulosis (by definition) and the nodules of large cell C-ALCL (20%) often spontaneously regress, healing with scarring. The therapeutic recommendations are given in Tables 3 and 4.

Sézary syndrome (SS)

Many retrospective studies on the treatment of SS contain inadequate information on the diagnostic criteria and staging of the disease, making a comparison of the therapeutic options impossible (Table 5).

therapy of CBCL: low-grade primary cutaneous B-cell lymphoma (follicular lymphoma, marginal zone lymphoma)

The low-grade CBCL are morphologically similar to MALT (mucosa-associated lymphoid tissue) lymphomas and therefore described by some authors as SALT (skin-associated lymphoid tissue) lymphomas. The prognosis of these tumors is in general very favorable. In those cases in which infectious agents (such as *Borrelia burgdorferi* DNA) can be identified, an initial therapeutic attempt with doxycycline (100 mg b.i.d. for 3 weeks) and assessment of the clinical response is recommended. Distinguishing between low-grade CBCL and reactive B-cell pseudolymphomas can be quite difficult; even clonality studies cannot with certainty separate the two entities. Therapeutic recommendations are given in Table 6. Rituximab should only be employed in those cases in which CD20 expression has been proved histologically.

large cell B-cell lymphoma

This group of CBCL has a worse prognosis than those with follicular differentiation. There are no large studies dealing with these tumors, making the formulation of guidelines difficult. First-line treatments of PCLBCL leg type is R-CHOP and radiation therapy for solitary lesions.

therapy of non-CD4+/CD56+ hematodermic neoplasm

In general, aggressive polychemotherapy regimens are recommended in these neoplasms of plasmacytoid dendritic cells and other rare unclassified CL, although no large studies or therapeutic comparisons are available.

follow-up

The interval between visits for patients with CL must be adjusted to the clinical findings. In those with early disease (stage Ia, Ib), evaluation every 6–12 months is reasonable. In advanced disease (stage III–IV), often the patient must be checked every 4–6 weeks to assess the therapeutic response.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Table 3. Therapy recommendations for lymphomatoid papulosis (level of evidence III)

Degree of involvement	First-line therapy	Second-line therapy
Solitary or localized lesions	Excision	
	Observation	
Multifocal lesions	Observation	IFN
	PUVA	IFN + retinoid
	Methotrexate up to 20 mg/weekly	Bexarotene

Table 4. Therapy recommendations for large cell CD30+ C-ALCL (level of evidence III)

Degree of involvement	First-line therapy	Second-line therapy
Solitary or localized lesions	Excision	Methotrexate
	Radiation therapy	IFN
Multifocal lesions without spontaneous remission	Methotrexate	Radiation therapy, IFN

Table 5. Therapy recommendations for Sézary syndrome (level of evidence IV)

First-line therapy	Second-line therapy
PUVA + IFN	Bexarotene
Extracorporeal photopheresis	Chlorambucil/corticosteroids
HN2	Low-dose methotrexate
	CHOP polychemotherapy
	Denileukin–diftitox
	Vorinostat
	Total skin electron beam therapy

Table 6. Therapy recommendations for low-grade primary cutaneous B-cell lymphoma (follicular lymphoma, marginal zone lymphoma) (level of evidence IV)

Degree of involvement	First-line therapy	Second-line therapy
Solitary lesions	Excision	Intralesional
	Antibiotics (only in PCMZL)	Intralesional corticosteroids
	Radiation therapy	
Multiple lesions	Antibiotics (only in PCMZL)	Intralesional IFN-α
	Radiation therapy	Intralesional rituximab
		i.v. rituximab

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