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Treatment of Cutaneous Lymphomas: Today and Tomorrow

D.S. Mestel, M. Beyer, M. Steinhoff and W. Sterry
Department of Dermatology Venereology and Allergy. Skin Cancer Center. Charité Universitaetsmedizin Berlin. Germany.

Abstract. There exist many skin-directed and systemic immunomodulating or cytotoxic treatment options for primary cutaneous T- and B-cell lymphomas. However, especially in advanced stages conventional therapies only end in a transient remission without curative results unable to prolong overall survival. Over the last twenty years the high need of new therapeutic strategies resulted in the development of emerging drugs targeting more tumor specific, like monoclonal antibodies, histone-deacetylase inhibitors, proteasome inhibitors, or fusion proteins.
This article aims to discuss the conventional treatment modalities as well as new therapeutic strategies, which passed already through clinical trials showing promising results in the treatment of primary cutaneous lymphomas.

Key words: primary cutaneous lymphoma, conventional therapy, emerging drugs, monoclonal antibody, HDACI, chemotherapy.

TRATAMIENTO DE LOS LINFOMAS CUTÁNEOS: HOY Y MAÑANA

Resumen. Existen varias opciones terapéuticas dirigidas a la piel y sistémicas, inmunomoduladoras o citotóxicas, para los linfomas cutáneos primarios de células B y T. No obstante, las terapias convencionales sólo consiguen una remisión transitoria sin resultados curativos, incapaces, por tanto, de prolongar la supervivencia global, especialmente en fases avanzadas. En los últimos 20 años, debido a la creciente necesidad de nuevas estrategias terapéuticas, se han desarrollado fármacos con dianas tumorales más específicas, como los anticuerpos monoclonales, los inhibidores de la histona deacetilasa, los inhibidores del proteosoma o las proteínas de fusión.
Este trabajo tiene por objetivo discutir las modalidades terapéuticas convencionales, así como las nuevas estrategias terapéuticas que ya han mostrado resultados prometedores para el tratamiento de los linfomas cutáneos primarios en ensayos clínicos.

Palabras clave: linfoma cutáneo primario, terapia convencional, fármacos emergentes, anticuerpo monoclonal, inhibidores de la histona deacetilasa, quimioterapia.

Introduction

Primary cutaneous lymphomas (PCL) are clonal proliferations of malignant lymphocytes, belonging to extranodal non-Hodgkin lymphomas (NHL). Per definition they are localized in the skin without any evidence of extracutaneous manifestation at the time of diagnosis. They can be divided in primary cutaneous T- and B-cell lymphomas (CTCL and CBCL). PCL have in most cases a completely different clinical behavior and prognosis compared to histological similar systemic lymphoma, which may affect the skin secondarily. This is of special importance in regard to choice of treatment. Mycosis fungoides (MF) including its leukemic variant Sézary syndrome (SS) is the most common type of all PCL with about 50 % followed by the group of CD30-positive lymphoproliferations (CD30-postive anaplastic large cell T-cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP) comprising about 20% of all PCL[1-5]. Compared to CTCL the group of CBCL is less common and constitutes about 20% to 25% of PCL. The different subtypes of PCL are summarized in table 1[6]. The revised staging system for MF and SS is demonstrated in table 2[7]. With an incidence of 1 to 2 cases per 100.000 population a year PCL are rare but their incidence is increasing. However, the exact pathomechanisms of these diseases are unknown[8].

Correspondence:
Dominik S. Mestel.
Department of Dermatology, Venereology and Allergy.
Skin Cancer Center.
Charité Universitaetsmedizin Berlin.
Charitéplatz 1.
D-10117 Berlin (Germany)
dominik.mestel@charite.de

Table 1. Different subgroups of primary cutaneous lymphomas

	WHO-EORTC classification	*Frequency (%)*	*5-year-survival (%)*
Indolent primary cutaneous T-cell lymphomas	Mycosis fungoides MF	44	88
	Folliculotropic MF	4	80
	Pagetoid reticulosis	< 1	100
	Granulomatous slack skin	< 1	100
	Primary cutaneous anaplastic large cell lymphoma	8	95
	Lymphomatoid papulosis	12	100
	Subcutaneous panniculitis-like T-cell lymphoma	1	82
	Primary cutaneous $CD4^+$ small/medium pleomorphic T-cell lymphoma	2	75
Aggressive primary cutaneous T-cell lymphomas	Sézary syndrome	3	24
	Primary cutaneous NK/T-cell lymphoma	< 1	NR
	Primary cutaneous $CD8^+$ T-cell lymphoma	< 1	18
	Primary cutaneous γ/δ T-cell lymphoma	< 1	NR
	Primary cutaneous peripheral T-cell lymphoma, unspecified	2	16
Indolent primary cutaneous B-cell lymphomas	Primary cutaneous marginal zone B-cell lymphoma	7	99
	Primary cutaneous follicle center cell lymphoma	11	95
Intermediate primary cutaneous B-cell lymphoma	Primary cutaneous diffuse large B-cell lymphoma, leg type	4	55
	Primary cutaneous diffuse large B-cell lymphoma, others	< 1	50
	Primary cutaneous intravascular large B-cell lymphoma	< 1	65

MF: mycosis fungoides; NR: not reached.

The majority of PCL are indolent malignancies. MF in early stages, CD30-positive T-cell lymphomas, as well as CBCL (marginal zone lymphoma, MZL and follicle centre cell lymphoma, FCL) show a disease-specific 5-year survival rate of more than 90 %. However there are also PCL showing a more aggressive course e.g. the diffuse large B cell lymphoma, leg type (DLBCL-LT), MF with extracutaneous manifestation, SS or rare entities like NK/T-cell lymphoma, nasal type[9-12]. By today no curative approach for PCL exists. In early as well as in advanced disease, there is evidence that aggressive therapies, like multi-agent chemotherapy only result in a transient remission without an improvement of overall survival. Therefore the main aims of treatment include clearance of skin lesions going along with maintenance or improvement of quality of life and prolongation of disease-free survival. A stage-adapted sequential therapeutic approach is recommended. External, skin directed therapies are commonly used in patch or plaque stages of CTCL or solitary skin lesions of CBCL. Systemic therapies are mostly reserved for advanced stages or multiple lesions as well as involvement of sites undesirable for local therapy[13,14]. The current EORTC (European Organization for Research and Treatment of Cancer) consensus recommendations are summarized in table 3 for MF and in table 4 for SS[15]. This article aims to give an overview about the currently existing as well as upcoming emerging new therapies of the above mentioned most frequent PCL.

Treatment of Mycosis Fungoides and Sézary Syndrome Today

Topical Treatment of Mycosis Fungoides and Sézary Syndrome Today

PCL are diseases with clonal lymphoma cells, which home – at least in initial stages – exclusively to the skin. Hence CTCL lesions may appear all over the body. Skin-directed therapies, e.g. topical corticosteroids, phototherapy like PUVA or narrow-band UVB, skin-applied chemotherapeutics like nitrogen mustard (NH_2, mechlorethamine hydrochloride) or carmustin/BCNU, or radiation of the body surface are the most common used first-line treatment op-

Table 2. Staging of mycosis fungoides and Sézary syndrome

Stage	*IA*	*IB*	*IIA*	*IIB*	*III*	*IIIA*	*IIIB*	*IVA$_1$*	*IVA$_2$*	*IVB*
T	1	2	1 or 2	3	4	4	4	1-4	1-4	1-4
N	0	0	1 or 2	0-2	0-2	0-2	0-2	0-2	3	0-3
M	0	0	0	0	0	0	0	0	0	1
B	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0	1	2	0-2	0-2

Skin (T = tumor)
T1 patch/papules/plaque ≤ 10 % of body surface
T2 patch/papules/plaque > 10 % of body surface
T3 one or more tumors (≥ 1 cm diameter)
T4 erythroderma (confluence of erythema covering ≥ 80 % of body survace)

Node (N = lymph node)
N0 no clinically abnormal peripheral lymph nodes
N1 clinically abnormal peripheral lymph nodes/dermatopathic lymphadenopathy
N1a clone negative
N1b clone positive
N2 clinically abnormal peripheral lymph nodes/presence of cerebriform nuclei > 7.5 m
N2a clone negative
N2b clone positive
N3 clinically abnormal peripheral lymph nodes/partial effacement of LN architecture; many atypical cerebriform mononuclear cells; complete effacement

Visceral (M = metastasis)
M0 no visceral organ involvement
M1 visceral involvement

Blood (B = blood)
B0 absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sézary) cells
B0a clone negative
B0b clone positive
B1 low blood tumour burden: > 5 % of peripheral blood lymphocytes are atypical (Sézary) cells but do not meet the criteria of B2
B1a clone negative
B1b clone positive
B2 high blood tumour burden: ≥ 1,000/ l Sézary cells

tions in early stages of disease presenting with patches and plaques (stage IA, IB)[16-21].

Phototherapy - PUVA (Psoralen plus UVA, 320-40 nm) or UVB Radiation

Eight-methoxy-psoralen (8-MOP), a photosensitizer is applied either as tablets or in topical formulations like cream or as aqueous solution for a bath. Epidermal cells incorporate 8-MOP, which induces DNA chain breaks after photoactivation by UVA-radiation resulting in cell death. A further option in the treatment of MF is the irradiation with UVB light either as broadband (290-320 nm), or as narrow band (311 nm), the last being less irritative. UVB therapy also results in good clinical responses but its efficacy, especially for plaque disease, may not be as effective as PUVA[22,23]. Excellent clinical responses up to complete remissions can be achieved also in recurrent disease. Patients, in particular those with repetitive courses of PUVA therapy should be instructed to exert preventive measures to minimize the increased risk of cutaneous epithelial neoplasm and cataract formation[24,25].

Extracorporeal Photopheresis

Extra-corporeal photopheresis (ECP) is a special type of phototherapy usually being indicated for the treatment of erythrodermic CTCL like SS. In patch and plaque stage MF (stage IB) ECP has been shown to be non effective[26]. Reliable parameters for a good response to ECP are leucocyte counts < $2.0 \times 10^9/l^{-1}$, presence of 10-20 % Sézary cells and lack of prior chemotherapy[27]. During the ECP procedure leucocytes are filtered from the blood by a special device via an intravenous line. The photosensitizing agent 8-MOP is added extracorporeal to the enriched leucocytes followed by irradiation with UVA light. The treated cells are thereafter re-infused to the patient. The first improvement may be observed as early as 6 weeks after

Table 3. Recommendations for first- and second-line treatments of mycosis fungoides

	MF IA – IIB	*MF IIB*	*MF IIII*	*MF IVA -IVB*
First-line	PUVA	PUVA + INF-	PUVA + IFN-	ECP
	UVB (patches only)	TSEB, superficial X-irradiation	IFN- monotherapy	IFN-
	Topical corticosteroids	Retinoids + INF-	MTX	Denileukin diftitox
	Localised radiotherapy	PUVA + retinoids	TSEB/X-irradiation	Chlorambucil/prednisone
	TSEB (≤ 3 treatments)		Carmustine	
	Carmustine		Nitrogen mustard	
	Nitrogen mustard		ECP	
			PUVA + retinoids	
Second-line	Oral bexarotene	Oral bexarotene	Oral bexarotene	HDACI (vorinostat)
	INF- monotherapy	Denileukin diftitox	HDACI (vorinostat)	
	INF- + retionoids	Chemotherapy	Chemotherapy	
	Denileukin diftitox	HDACI (vorinostat)		
	Low-dose MTX			
	INF- + PUVA			
	Retinoids + PUVA			
	Bexarotene + PUVA			

CHOP: cyclophosphamide, hydroxyldaunorubicin (adriamycin), oncovin (vincristine), prednisone; ECP: extracorporeal photopheresis; HDACI: histone deacetylase inhibitor; IFN- : interferon- ; MF: mycosis fungoides; MTX: methotrexate; PUVA: psoralen plus ultraviolet-A irradiation; SS: Sézary syndrome; TSEB: total skin electron beam therapy; UVB: ultraviolet-B irradiation.

start of treatment. Varying response rates of 43-100% have been reported by different groups[28]. The median time to response is 5-6 months[29]. Overall, this treatment is very well tolerated without serious adverse events[30,31].

Skin Radiation

Radiosensitivity of lymphocytes is well known. Therefore radiotherapy is an option, which can be applied localized for individual lesions in form of a superficial X-irradiation or generalized as total-skin electron-beam (TSEB) radiation for skin-limited disease, including tumor stage. The recommended dosage for localized superficial radiation of individual lesions usually is 30 cGy. However, recently quite good response rates have been reported with low-dose 8 cGy radiation[14]. Also TSEB shows high complete response rates up to 80%-90%. Patients in stages IA or IB show a median duration of remission of more than 3 years. For patients with erythroderma (stage III) or tumors (stage IIB) the median duration of response is 1 year and less than 6 months, respectively. According to the EORTC treatment guidelines for the use of TSEB the total treatment dose is usually 30-36 cGy over 8-10 weeks[13].

Table 4. Recommendations for first- and second-line treatments of Sézary syndrome

	Sézary syndrome
First-line	ECP
	IFN-
	Denileukin diftitox
	Chlorambucil/ prednisone
Second-line	Oral bexarotene
	Chemotherapy
	Alemtuzumab
	MTX

ECP: extracorporeal photopheresis; IFN- : interferon- ; MTX: methotrexate; SS: Sézary syndrome.

Chronic and acute adverse events are in general skin-limited and encompass loss of body hair, as well as general atrophy of sweat glands and skin, radiodermatitis, and edema. By fractionating the total dose adverse events can be reduced[32,33].

Systemic Treatment of Mycosis Fungoides and Sézary Syndrome Today

Interferon-alpha

A number of clinical trials demonstrated efficacy of interferon-alpha in CTCL with overall response rates between 40% and 80%[34]. The dose of subcutaneously applied interferon-alpha usually amounts 3 million units (MU) three times per week in the beginning. The dose of the single application is stepwise increased up to 9 MU, as longs as no dose limiting toxicity occurs. Responses induced by interferon-alpha are gradual and it takes about 3 to 6 months until the maximal response is achieved. Hereafter interferon-alpha might be reduced to a maintenance dose of 1 MU per day. Skin-limited disease (stage I and II) shows more long-lasting and better response rates than advanced stages (stage III and IV)[35]. The most common dose-limiting toxicity is a dose-related flu-like syndrome, which is usually decreasing over time or can be alleviated by dose reduction. In daily practise, interferon-alpha is usually combined with other treatment modalities, i.e. PUVA and topical corticosteroids in stage IB or ECP and rexinoids in erythrodermic patients (see below). If a monotherapy with interferon-alpha induces only PR, the addition of either of the mentioned therpeutic options may improve responses[36,37].

Retinoids/Rexinoids – Bexarotene

Intracellular receptors of the steroid hormone family regulate a great diversity of cellular processes like differentiation, proliferation and apoptosis[38]. The retinoic acid receptors (RAR) and the retinoid X receptors (RXR) are part of the group of steroid hormone receptors[39]. Bexarotene, a so-called rexinoid is the first synthetic retinoid which selectively binds RXR[40,41].

By combining efficacy and tolerability of bexarotene the optimal daily dose was evaluated to be 300 mg/m^2. Best results could be demonstrated for stages IA to IIA with an ORR of 54%, while advanced stages (IIB to IVB) showed an ORR of 45%. Patients also experienced a reduction of pruritus and scaling. Improvement typically occurs by week 12 of therapy. The most common side effects are elevation of blood triglycerides and cholesterol, as well as hypothyroidism, leucopenia, pruritus, and skin disorders like eczema. Concomitant medications like lipid-lowering drugs are required to manage high lipid-levels. Low levels of thyroid-stimulating hormone (TSH) may occur within a few weeks after initiation of treatment. The symptoms of hypothyroidism may be similar to symptoms associated with CTCL like fatigue and a sensation of cold. Supplementation with levothyroxin moderates these symptoms and helps to improve the tolerance to bexarotene treatment[42].

Fusion Molecules - Denileukin Diftitox (ONTAK®)

Denileukin difitox is a recombinant fusion protein, composed of the receptor-binding domain of the human interleukin-2 (IL-2) and the catalytic domain of the diphtheria toxin[43]. This molecule binds to the interleukin-2-receptor (IL-2-R) which is expressed by activated lymphocytes and monocytes and is subsequently endocytosed into the cell. After enzymatic release of the diphtheria toxin from the IL-2-domain into the cytoplasm protein-synthesis will be inhibited[44]. This drug is administered intravenously in doses of 9 or 18 g/kg body weight once a day on 5 consecutive days every 3 weeks for up to 8 cycles. In a double blinded phase III trial 144 relapsed CTCL patients were treated either with denileukin diftitox with 1 of the above mentioned 2 doses or with placebo. The ORR was 49.1% (CR 9.1%) and 37.8% (CR 11.1%) for 18 mg/kg and 9 mg/kg, respectively. Median times to response were 92 days and 120 days for 18 g/kg and 9 g/kg, respectively. The median durations of response were 971 days, 794 days, and 124 days for 18 g/kg, 9 g/kg, and placebo, respectively. A potentially severe side-effect being observed in about 25% of patients, especially in hypalbuminemic patients, is the capillary leak syndrome. Infusion-related side effects like chest or back pain and dyspnea can be minimized by premedication with corticosteroids, paracetamol and antihistamines[45,46].

Chemotherapies

Although CTCL respond readily to diverse chemotherapies there is no documented impact on disease outcome. Therapeutic regimens include single agents and a variety of combinations like CHOP and EPOCH[47-49]. Combinations result in higher response rates, but imply stronger adverse events regarding the higher risk of infectious complications and myelosuppression. Therefore polychemotherapy should be reserved as third- or fourth line therapy for advanced stage lymphoma. In general, chemotherapy, usually single agents, is applied as second-line treatment in MF stage IIB or higher and SS. Two single agents with an acceptable safety profile and good response rates in CTCL are presented in the following part.

Pegylated Liposomal Doxorubicin

Compared to unpegylated doxorubicin an enhanced anti-tumor activity due to higher intracellular concentrations and half-life period as well as less toxicitiy can be achieved by encapsulating this agent into liposomes. Its efficacy and safety profile has been evaluated in several clinical studies

in patients with MF and SS[50]. Pegylated liposomal doxorubicin is administered intravenously once a month in a dosage of 20 mg/m^2 body surface. In two clinical trials ORR were 84.2 % and 88 % with CR of 42.1 % to 44 %, respectively. The median time to response was 3 months, while the median progression-free survival lasted 19 months. It could be demonstrated that pegylated liposomal doxorubicin is well tolerated with grade-3 and -4 toxicities in only 11 % of the treated patients[51,52]. Due to the high response rates and mild toxicities pegylated liposomal doxorubicin represents a good treatment option in refractory CTCL patients with advanced stages.

Gemcitabine

Gemcitabine (gemcitabine-triphosphate) is a pyrimidine-analogon which replaces cytidine during DNA-replication leading to DNA chain breaks[53,54]. Its efficacy was established in CTCL patients, most of them with MF. In a dosage of 1200 mg/m^2 gemcitabine was administered intravenously on days 1, 8, and 15 of a 28-day schedule for a maximum of 6 cycles. ORR of 75 % were observed (CR: 22 %, PR: 53 %). The median time to progression was 10 months. Documented side-effects in this study were grade-3 to -4 thrombocytopenia and neutropenia in 12 % and 16 % of patients, respectively. However, in a recently published retrospective multicenter trial of gemcitabine in advanced CTCL including 14 MF and 6 SS patients, a higher incidence of side-effects has been reported. In this trial, 30 % of patients showed grade-3 or 4 neutropenia and 6 severe adverse events, e.g. one haemolytic-uraemic syndrome and 1 severe capillary leak syndrome have been reported. In our experience, gemcitabine is a quite effective agent with an acceptable toxicity profile. However, patients should be monitored closely, in particular those patients who previously received treatment with chemotherapeutic or leukocyte-depleting agents like alemtuzumab.

Treatment of Mycosis Fungoides and Sézary Syndrome Tomorrow

Cytotoxic Chemotherapy – Forodesine

The novel immunosuppressant forodesine is selectively directed against T-cells. Its mechanism of action complies with the inhibition of the purine nucleoside phosphorylase (PNP), which recycles and dephosphorylates deoxyguanosine (dGuo) to guanine and deoxyribose-1-phosphate. Apoptosis is initiated by an accumulation of deoxyguanosine triphosphate (dGTP), following the inhibition of PNP[55-57]. In an open label phase I/II trial of orally administered forodesine the optimal dosage was assessed with 80 mg/m^2. The treated group included 36 CTCL patients in stage IB or higher. The ORR was about 40 % for SS and MF. The median time to response was 42 days, and the median duration of response 127 days. Most common adverse events of grade-3 or higher included diarrhea, pneumonia, edema, and rash. A grade-3 lymphopenia could be observed in 71 % with low CD4-counts in 31 %. Other grade-3 hematopoietic and clinical laboratory toxicities were neutropenia, anemia, as well as elevations of liver parameters[58]. Because of the good response rates with acceptable side effects a multicenter phase-II study is currently ongoing[59].

Monoclonal Antibodies

Zanolimumab

The fully human monoclonal antibody zanolimumab is directed against the CD4-antigen expressed by T-helper cells, malign CTCL cells, as well as in lower levels by monocytes, and macrophages. Zanolimumab decreases T-cell activation dose-dependently by interfering with the binding of the CD4 protein to its ligand, namely the major histocompatibility complex class II-molecule (MHC-II)[60,61]. *In-vitro* the CD4-expressing cells are undergoing cell death by antibody mediated cellular cytotoxicity. Patients with MF and SS were treated intravenously with zanolimumab in clinical phase-II trials. While MF patients demonstrated a dose-dependant increase in ORR up to 75 % for 980 mg the ORR was only about 20 % irrespective of the dose in SS patients. The median duration of response for MF was up to 91 weeks for the high-dose levels. Infusion-related side effects, like a cytokine release syndrome can be controlled with a premedication of acetaminophen. Other adverse events include dermatitis and infectious complications, mostly being low-grade and localized to the skin or the upper respiratory tract. The reactivation of cytomegalovirus (CMV) resulting in pneumonia was observed in one case. Beside a significant dose-related decrease of CD4-expressing T-cells no decrease in numbers of monocytes was found. Hematological and clinical chemistry changes were sporadic, mild, and transient. Taken the data of these two studies together zanolimumab is a well tolerated drug with good potency in the treatment of CTCL[62-65].

Alemtuzumab

The humanized monoclonal IgG antibody alemtuzumab targets CD52. This antigen is expressed by benign and malign T- and B-cells. Further CD52-expressing cells encompass monocytes, and granulocytes[66]. The mechanisms of action are antibody dependent cellular cytotoxicity, complement induced lysis, and induction of apoptosis[67].

Alemtuzumab was administered intravenously to MF and SS patients in doses of 30 mg three times weekly for a maximum of 12 weeks and subcutaneously to patients with SS in doses up to 15 mg[68-70]. For MF ORR differed from 30% to 50%, while it was nearly 86% for SS. Sézary-cells were cleared from the blood in 86% of SS patients. The results of the different studies clearly demonstrated a higher benefit of alemtuzumab for patients with erythroderma than for patients with plaques or tumors. Furthermore a significant reduced pruritus was reported. The median time to relapse was 12 months. Infusion or injection related-side effects like hypotension, urticaria, and bronchospasm, as well as fever, and rigor could effectively be controlled by a premedication of paracetamol and antihistamines and are less pronounced after subcutaneous application. Patients have to be monitored for severe neutropenia. To prevent opportunistic infections patients should obtain prophylaxis with cotrimoxazole and valaciclovir. Despite prophylaxis, serious infectious complications like reactivation of cytomegalovirus (CMV) or fatal pneumonia occured[71]. The cardiac toxicity of alemtuzumab is controversially discussed[72,73]. Taken together alemtuzumab is an option for patients with SS who experience a progress during or after standard therapies. The dose should be adjusted to the blood leukocyte counts and kept as low as possible to minimize the risk of infectious side effects. However, patients have to be controlled thoroughly throughout the treatment and until recovery of CD4 helper T cell numbers.

Histone Deacetylase Inhibitors (HDACIs)

Within recent years there is growing evidence that not only genetic but also epigenetic alterations like deacetylation of histones and transcription factors are crucial to the onset and progression of cancer. Two contrarious enzymatic pathways regulate this system, namely the histone acetyl transferases (HATs) and histone deacetylases (HDACs). Acetylated histones convey DNA transcription, while deacetylated histones keep the DNA in a transcriptional inactive state. An inhibition of deacetylases enhances the acetylated status of histones followed by a facilitation of gene-transcription, which is involved in cell differentiation, cell cycle arrest and apoptosis[74-77]. In the United States of America vorinostat has already been approved in 2006 for the treatment of refractory CTCL, while romidepsin, panobinostat, and belinostat are still undergoing different clinical trials. The group of HDACIs has a lot of common adverse events including fatigue, gastrointestinal symptoms like diarrhea, nausea, and dysgeusia. Hematologic findings are thrombocytopenia, and anemia[78]. A very important and controversial discussed topic is the development of QTc interval prolongations and ventricular tachycardia which are going along with an increased risk of fatal arrhythmia. To date it is not known, if the mechanisms which cause the cardiac toxicity are directly or indirectly induced by HDACIs[79,80]. It could be demonstrated *in-vitro* and *in-vivo* that vorinostat (suberoylanilide hydroxamic acid, SAHA) may directly induce cell death in several malignancies including CTCL[81-83]. Tolerability and efficacy of orally administered vorinostat (400 mg/day) were evaluated in two open label phase II multicenter trials on MF and SS patients with a relapsing course. In both trials ORR were similar with about 30%[84,85]. About one-third of all patients described a relieved pruritus. The median time to response was 56 days and the median time to progression 148 days for all patients.

After promising results of a phase I trial with romidepsin (depsipeptide, FR901228) in the treatment of CTCL a phase II trial was performed including 42 CTCL patients[86-89]. The dosage was 14 mg/m^2 administered on days 1, 8 and 15 of a 28 day cycle. The ORR of romidepsin was about one-third of all patients and therefore comparable to vorinostat. In a phase I trial of panobinostat (LBH589) an ORR of 60% could be demonstrated in the treatment of CTCL (n = 10). Therefore this HDACI is actually resided in a multicenter phase II trial. Panobinostat is an orally formulation administered 3 times weekly in a dose of 20 mg[90]. Most important adverse events were reversible ECG-changes (QTc prolongations)[91,92]. Belinostat (PXD101) is a HDACI that is administered intravenously (1000 mg/m^2) over 30 minutes on days 1 to 5 of a 21 day cycle. Within a median of 2 cycles an ORR of 25% could be seen, while the duration of response was up to 39 weeks. Pruritus clearly improved. Important serious adverse events included one fatality because of ventricular fibrillation[93].

Proteasome Inhibitor – Bortezomib

Misfolded and damaged intracellular proteins are normally eliminated by the 26S-proteasome, amongst other mechanisms. Blocking of this proteasome by the reversible inhibitor bortezomib causes an intracellular accumulation of defect proteins resulting in the activation of the heat shock protein response, which consequently ends up in cell death[94]. Furthermore bortezomib inhibits NF- B activation, which is known to be important for the resistance to apoptosis of CTCL cells[95]. The antitumor activity of bortezomib in CTCL was demonstrated in a phase II clinical trial. The ORR was 67% with 2 histologically confirmed CR, one of them lasting longer than 12 months. Durable PR lasted from 1 to 14 months. Bortezomib was given intravenously in a dose of 1.3 mg/m^2 on day 1, 4, 8 and 11 of a 21 day cycle for up to 6 cycles. The most important complication was a reversible grade-1 to -3 sensory neuropathy which was observed in 50%. Hema-

tological grade-3 changes included neutropenia, and thrombocytopenia[96]. Beside a quite safe profile in regard to adverse events bortezomib demonstrated great efficacy as a single agent in patients with relapsed and therapy-refractory CTCL and PTCLU.

Stem Cell Transplantation

Non-chemotherapeutical alternatives in the treatment of MF and SS include autologous or allogenic hematopoietic stem cell transplantations (HSCT)[21,97]. HSCT are well experienced in other systemic lymphomas but with respect to PCL the knowledge about its efficacy is still limited to a few series and case reports. Autologous HSCT may induce CR in the majority of patients but with only short lasting responses. Twenty cases demonstrated a safe profile with only one death related to transplantation and an anti-CTCL effect with CR in 18 patients. Notwithstanding these great response rates the effect was short with a median time to relapse from less than 100 days[98]. Relapses may be induced by a recirculation of the malignant T-cells contaminating the graft. In fact of the short relapse-free survival a potential benefit for patients treated with autologous HSCT could be the achievement of a less extensive disease with an enhanced quality of life. By perfoming an allogenic HSCT from healthy donors durable remissions for more than 3 years can be achieved in about 66 %, potentially mediated by a graft-versus-lymphoma effect (GVL). This effect is explicable since durable remissions are associated with a chronic graft versus host disease (GVHD) and furthermore relapses can be triggered by the immunosuppressive treatment against the GVHD. By reducing immunosuppression remissions can be re-induced. In a total of 21 heavily pretreated cases encouraging results could be evaluated dependant to GVL[98]. These promising results may enhance the expected median time of survival. A 27 year old patient with MF in stage IVA resulted in CR after HSCT, while she relapsed 9 months after intervention. By reducing immunosuppressive medication and application of further lymphocyte infusions clinical and histological remissions could be re-achieved, indicating the GVL-effect[99]. The first case from 1994 with advanced MF had a recurrence-free survival of up to 6 years[100]. In further 10 reported patients 8 were alive without severe limitations of quality of life due to the disease over a median time of 57 months[98]. One 22-year old patient with a heavily pretreated SS underwent allogenic HSCT from a HLA-identical donor and evolved an acute and chronic GVHD. Thirty-six months after transplantation he was still in CR with no detectable Sézary cells, lymphadenopathy, or clonal T-cell receptor rearrangements[101]. The published data of allogenic compared to autologous HSCT in CTCL have demonstrated long-lasting and reproducible remissions. Therefore intensive research and an increased collection of more cases of this encouraging therapeutic modality have to be investigated in the close future.

Treatment of Cutaneous CD30$^+$ Lymphoproliferative Disorders Today

CD30$^+$ lymphoproliferative disorders comprising LyP and C-ALCL in general show a favorable prognosis. Spontaneous regression of lesions is a diagnostic phenomenon in LyP and may be also observed in C-ALCL. In LyP patients with regional or limited disseminated disease whose quality of life is not affected an 'observant policy' is an acceptable procedure. For patients with localized LyP who have a desire for therapy or patients with solitary C-ALCL radiotherapy is the treatment of choice. In a retrospective trial efficacy and safety of radiotherapy as first-line treatment was evaluated in 8 C-ALCL patients. The dosage ranged between 34 to 44 Gy, in 2- to 3-Gy fractions with 5 fractions weekly. The typical dose was applied to a depth of 1 cm under the lesion and a safety margin of 2 to 3 cm were treated with 6 MeV electrons in 7 patients, while one patient received 6 MV photons. Long-lasting CR was observed 100 % (8/8 patients) over a median follow-up time of 12 months. Grade-1 to 2 dermatitis occurred in all patients[102,103]. Patients with LyP and C-ALCL presenting with multiple or disseminated skin lesions can be treated systemically with low-dose methotrexate (five to 20 mg once a week)[104]. A further treatment option seems to be photodynamic therapy (PDT), which has shown promising results in the treatment of therapy-refractive LyP[105].

Low-Dose Methotrexate

Forty-five patients with CD30$^+$ primary cutaneous lymphomatoid disorders were treated with methotrexate orally in a median dose of 20 mg per week (range, 10 to 60 mg). The median duration of methotrexate therapy was 39 months. The clinical amelioration was achieved shortly after the start of treatment. A Long-term control could be accomplished in 87 % (39/45) with doses given at median 10- to 14-day intervals. Adverse events were in general of mild character and transient with fatigue (47 %), nausea (22 %), diarrhea and gastrointestinal symptoms (10 %), as well as early hepatic fibrosis in 5 of 10 patients, who achieved methotrexate for more than 3 years (range, 38 to 111 months). Laboratory aberrations included increased hepatic transaminase level (27 %), anemia (11 %), and leucopenia. Today in patients with CD30$^+$ cutaneous disorders low-dose metothrexate is the chemotherapeutic drug of choice because of its efficacy and tolerability in light of the benign prognosis of the diseases[104].

Treatment of Cutaneous CD30+ Lymphoproliferative Disorders Tomorrow

Monoclonal Antibodies CD30-Antibody SGN-30, MDX-60

The CD30 antigen is expressed on cells of LyP and C-ALCL. The expression on Hodgkin lymphoma (HL) cells made this antigen an ideal target for monoclonal antibodies. SGN-30, a chimeric anti-CD30-antibody showed antitumor acitivity *in-vitro* and *in-vivo*[106,107]. Duvic et al performed a multicenter phase-II trial for 17 cutaneous CD30+ lymphoproliferative disorders. Patients achieved SGN-30 every 2 to 3 weeks intravenously at a dosage of 12 mg/kg for up to 3 cycles. Each cycle comprised of 6 administrations of SGN-30. One CR and 5 PR could be observed with 1 patient showing stable disease. The duration of response was more than 256 days for the CR and ranged from 56 up to 271 days for the PR. Preliminary data from this phase II study indicate SGN-30 as a well tolerated drug with good antitumor activity[108].

Treatment of Primary Cutaneous B-Cell Lymphomas Today

Radiotherapy

The radiosensitivity of CBCL is well known. Therefore radiotherapy is – beside surgical excision – the first choice of treatment especially in localized disease. Its efficacy could be demonstrated in a number of different trials[109,110]. In a recent retrospective multicenter analysis efficacy of first-line radiotherapy was evaluated for MZL (n = 25), FCL (n = 101), and DLBCL-LT (n = 27). The median dosage was 40 Gy (range, 20-46 Gy). A margin of at least 2 cm of healthy skin was included to the exposed irradiated area. CR could be seen in 99 % of all treated patients (151/153). The two non-responders were among the DLCBL-LT-group. During a median follow-up time of 62 months the relapse rates for MZL, FCL, and DLBCL-LT were 60 % (15/25), 29 % (29/101), and 64 % (16/25), respectively. The median relapse-free interval was 16 months (range, 3-144 months), and 12 months (range, 2-62 months) for MZL and FCL, respectively. The disease-specific survival (DSS) for MZL, FCL, and DLCBL was 95 %, 97 %, and 59 % and the 5-year overall survival (OS) was 90 %, 90 %, and 40 %, respectively. This retrospective study demonstrates again that radiotherapy should be the treatment of choice in localized MZL and FCL[111].

Excision

Beside radiotherapy surgical excision is another first-line therapy of CBCL presenting with solitary or some small nodules or plaques. For MZL complete responses could be reached by excision in 74 of 75 patients, while 43 % (32/75) relapsed. Similar results were found for patients with FCL who had a CR in 98 % (91/93) and a relapse rate in 40 % (36/91). For both subtypes no details of excision margins or relapse sites were provided in these studies[112].

Intralesional Interferon-Alpha

Both MZL and FCL showed good response rates to intralesional interferon-alpha, which was injected in dosages from 1 to 6 Mio IU 3 times weekly. CR of 100 % could be observed for MZL (n = 8) and FCL (n = 7) after a median duration of treatment of 8 weeks. Both entities showed two relapses. Relapsed patients showed a further CR after re-treatment. In general adverse events could be counted as mild and this treatment option may be used in difficult areas to treat like faces, without resulting in scars[113-117].

Cytotoxic Chemotherapy

As MZL and FCL show an indolent clinical course cytotoxic chemotherapies should be reserved for patients with disseminated skin-lesions or relapses. Taken the data of different trials together treatment of 33 MZL patients with CHOP-like regimens resulted in a CR in 85 % but with high recurrence of 57 %[112]. Similar response rates were described for FCL. Eighty-eight of 104 FCL-patients in 8 trials who were treated with CHOP or COP showed a CR in 85 % while 42 of the 88 responding patients relapsed (48 %)[112].

In contrast to MZL and FCL the group of DLCBL-LT has a much worse prognosis so that many authors favor to treat this entity with a multi-agent chemotherapy like systemic lymphomas. The collected data of 32 cases treated with CHOP-like regimens showed CR in 81 % (26/32) while 54 % (14/26) relapsed. Combinations of anthracyline based chemotherapies and rituximab (see below) in the treatment of DLCBL-LT promises better response rates: 92 % (11/12) had CR and only 1 of them relapsed[112].

Monoclonal Antibodies - Rituximab Intralesional/Intravenously

The chimeric monoclonal antibody rituximab is directed against the CD20-antigen, which is expressed on all CBCL, as well as on normal B-lymphocytes. Rituximab

directly induces apoptosis and it further activates the complement cascade resulting in cell-lysis[118,119]. A retrospective trial including 15 patients (MZL = 5, FCL = 10) demonstrates excellent results for rituximab administered intravenously with 375 mg/m^2 weekly for 4 weeks. The ORR was 87 % with CR in 60 % and PR in 27 %. Responses could be observed within a median time of 30 days. The median duration of response was 24 months while seven patients were still in remission after a median follow-up time of 36 months[120]. Because of the efficacy and safety profile of systemically administered rituximab and promising results of intralesional injected rituximab a comparative trial between these 2 application forms was performed[121,122]. Eight patients with MZL and FCL obtained rituximab either intralesionally (n = 6) for 1 or 2 cycles with 10 to 30 mg per lesion 3 times a week or intravenously (n = 2) with 375 mg/m^2 once a week for 4 weeks. CR was achieved in 100 %, with 4 of the 6 intralesionally treated patients experiencing a relapse (67 %) within a mean of 6 months. The recurrent lesions showed a further response to a second intralesional cycle. The 2 intravenously treated patients were not bothered by a relapse during the follow-up time (18 to 24 months). In this study no adverse events did occur and therapy in general was well tolerated. Intralesional rituximab seems therefore to be a good alternative to radiotherapy or surgical excision in areas which are difficult to treat like face or scalp without the risk of alopecia or scars[123].

Treatment of Primary Cutaneous B-Cell Lymphomas Tomorrow

Combination of Rituximab and Chemotherapies

Of 13 intravenously treated DLCBL-LT patients only 5 demonstrated a CR. Therefore rituximab as single agent does not give the efficient results as it does for MZL and FCL[112]. In a retrospective review with 60 patients better response rates could be demonstrated by combining rituximab and anthtracycline-based chemotherapies. Fifteen percent (n = 9) received polychemotherapies without anthtracycline, 30 % (n = 18) anthracycline-based chemotherapies without rituximab, and 20 % (n = 12) anthracycline-based chemotherapies in combination with rituximab. Because rituximab treatment did not start before 2002 and only rarely before 2004 long term survival rates of more than 3 years could not be observed. But the 2 year-survival rate was 59 % for patients who did not additionally receive rituximab compared to 81 % for those patients who were treated with combinations of rituximab and anthracycline-containing polychemotherapies. The patients with a combined treatment achieved a CR in 91.6 % (11/12) compared to 62 % for patients receiving other therapy modalities. Ten of the 11 responders had no relapse after a median follow-up time of 19 months and 9 patients were still alive[124]. A possible explanation for the advantage of the combination therapy might be that rituximab is able to overcome Bcl-2-associated chemotherapy-resistance and most DLCBL-LTs do intensely express Bcl-2[125]. For people older than 80 years and patients with poor general condition an age-adapted R-CHOP schedule can be applied as data of the so-called R-mini-CHOP show increased response rates and survival times than elderly patients who were treated with the standard protocol of R-CHOP[126,127]. This might be explained by the lower adverse events rate in comparison to standard CHOP-regimens.

Radioimmunotherapy - Yttrium-90 ibritumomab tiuxetan (^{90}Y-IT)

Like mentioned above radiosensitivity of all CBCL is well known. Indeed local therapy is limited for patients with widespread disease or for difficult treatable localizations. Therefore a "systemic" radiation was developed by combining an anti-CD20-antibody with tiuxetan, a molecule that contains the radionuclide Yttrium-90 (^{90}Y; ibritumomab tiuxetan, IT). Its beta-radiation has only a length of run of 5 mm in soft tissues with a short half-life period of 67 hours. ^{90}Y induces apoptosis in adjacent tumor-cells by a so-called cross-fire effect compared to directly targeted cells by a single anit-CD20 antibody[128]. In a mono-centre pilot study performed by Maza et al (2008) efficacy and safety were evaluated for CBCL. Nine of 10 included patients had relapsing diseases (FCL: n = 8; DLCBL-LT: n = 2). A pre-treatment with rituximab (250 mg/m^2) was accomplished on days 1 and 8 to reduce non-malignant CD20-expressing cells and to decrease the splenic uptake. The rituximab-administration on day 8 was followed intravenously by a single dose of ^{90}Y-IT in a dosage of 11-15 MBq/kg. As pre-treatment patients obtained immediately before a litre of sodium-chloride 0,9 % solution, hydroxyhydrochloride (50 mg), and indomethacin (100 mg) to prevent infusion-related side effects. The CR was 100 % with ongoing remissions in 4 patients within a median follow-up time of 19 months. CR was achieved within a median time to response of 4.5 weeks. The median time to relapse was 12 months. The 2 patients with DLCBL-LT had recurrence after 7 and 12 months, respectively. Observed adverse events included reversible myelosuppression grade-3 to -4 including thrombocytopenia and neutropenia. Other symptoms included a transient decrease in general condition for about one week post-infusional, myalgia, and a reduction of bodyweight[129].

Conclusion

This article discusses existing conventional therapies as well as newly developed and emerging drugs in the treatment of PCL. Therefore it becomes apparent that treatment modalities for these diseases have been changed continuously in the last 15 to 20 years. There exist many conventional therapies for indolent courses of PCL, like early stages of MF, CD30+ LTD, MZL, and FCL that offer good responses even they may be of short duration and not curative. For advanced stages of MF or DLCBL-LT there are very little treatment modalities and "classical" single or multi-agent chemotherapies are still largely ineffective as they do not result in a prolonged overall and disease-free survival. Despite a dissatisfying efficacy cytotoxic therapies are often accompanied by serious adverse events, like myelosuppression or infectious complications. In contrast to these mentioned conventional treatment modalities and with respect to intense research and comprehension of the pathophysiology and pathobiochemistry of malignant cells, as well as their cell cycles a variety of new targets have been declared. They are especially concentrated on immunotherapeuticals like monoclonal antibodies or non-immunosuppressant agents, like the interleukin-2 fusion toxin denileukin diftitox. Other treatment options belong to substances modulating and interacting with different pathways of cell cycles, e.g. the promising group of HDACIs or proteasome inhibitors. All of them offer promising results as single agents or as possible combination partners of already existing therapies. Rituximab and CHOP-like regimens as monotherapeuticals offer good response rates in CBCL, while a combination of both, known as R-CHOP, is able to significantly increase response rates by regarding DLCBL-LT. The *in-vitro* detected reduced cell-survival under a combined treatment of denileukin-diftitox and the HDACI romidepsin seems to be very promising[130]. Therefore it would be of great interest, if combinations of the mentioned drugs would increase the single-agent efficacy in the treatment of PCL and studies should further be investigated in this field. These two combinations are just two examples of great interest to identify several synergistic combinations of newly admitted or existing therapies to possibly increase treatment success in PCL-patients. Despite research and development of the mentioned new treatment options the physiological role of some of these therapeutically targets, e.g. HDAC is not completely understood and response rates, as well as duration of responses, particularly in advanced stages of CTCL are still unsatisfactory. Knowledge of the exact mechanism would enable developing drugs targeting more tumor-specific and possibly identifying the right combination partner leading to a synergistic anti-tumor effect whereby an increased benefit and a decreased rate of adverse events will hopefully be achieved. This seems not only to be important for survival; hence patients with heavily pre-treated PCL report a reduced quality of their daily life[131].

Conflict of interests
Authors have no conflict of interests to declare.

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