New and experimental skin-directed therapies for cutaneous lymphomas

Farkas, A; Kemeny, L; French, L E; Dummer, R

Abstract: Primary cutaneous lymphomas (CLs) originate in the skin and should be differentiated from secondary skin infiltrates, which are manifestations of lymphomas of nodal or extranodal origin. These rare diseases include various lymphoproliferative disorders: cutaneous T-cell lymphomas, cutaneous B-cell lymphomas and some rare subtypes. As definitive cure is often not possible, it is important to control the disease and alleviate symptoms. Patients with early-stage disease limited to the skin usually require skin-directed therapies using topical agents including corticosteroids, chemotherapeutic drugs, bexarotene gel, electron beam therapy and phototherapy. Each of these are effective; however, all have some disadvantages and are associated with significant adverse events. In the field of skin-directed therapies there are interesting developments using antineoplastic compounds, the retinoid tazarotene, imiquimod, gene therapy products (adenovirus vector expressing gamma-interferon), the monoclonal anti-CD20 antibody rituximab, photodynamic therapy and 308-nm excimer laser to mention a few. This review highlights some of the promising new and experimental local therapies for primary CLs and focuses on their efficacy and side effects.

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New and Experimental Skin-Directed Therapies for Cutaneous Lymphomas

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Introduction

Cutaneous lymphomas (CLs) are the second most common non-Hodgkin lymphomas with an estimated annual incidence of 1 new case per 100,000 inhabitants [1]. Primary CLs by definition arise in the skin, while secondary CLs are manifestations of disseminated, primary nodal or extranodal lymphomas [2]. Primary CLs include a broad spectrum of clinically and histologically heterogeneous lymphoproliferative diseases with diverse pathogeneses and clinical manifestations. Around 80% of primary CLs are T-cell types (CTCL), 10–20% are B-cell types (CBCL), and the remaining number of CLs corresponds to rare entities, such as CD4+/CD56+ haematodermic lymphomas, deriving from type 2 dendritic cells. The diagnostic approach includes clinical, histological, immunohistochemical, imaging, haematological and molecular examinations [3].

Classification

The latest classification system presented by the World Health Organization (WHO) and by the European Organization for Research and Treatment of Cancer is compatible with the WHO classification for haematopoietic and lymphoid neoplasias, includes additional entities and respects the organ-specific features of primary CLs [4, 5]. This consensus classification system divides CLs into 3 groups: CTCL and cutaneous natural killer cell lympho-
mas, CBCL and precursor haematological neoplasms (table 1). Based on the different biological behaviour, CLs may be grouped into prognostic categories such as prelymphomatous ‘abortive’ disorders, definite malignant lymphomas of low-grade malignancy and definite malignant lymphomas of high-grade malignancy [3].

**Skin-Directed Therapies**

It is recommended to identify the clinicopathological entity as given both in the classification system and the prognostic category to provide essential information on the behaviour of CLs and to allow the planning of the therapeutic strategy. The recommended approach for treatment is to aim for disease control, since definitive cure is usually not possible. Classical therapeutic modalities can be divided into topical or systemic. Table 2 shows a brief summary of the various standard topical treatment options, which have been reviewed earlier elsewhere [6]. In more advanced stages, various systemic treatment options such as glucocorticoids, extracorporeal photopheresis, recombinant α-interferon (IFN-α), retinoids, chemotherapeutic agents, bone marrow transplantation, fusion toxin denileukin difitox, histone deacetylase inhibitors, purin nucleoside analogue, monoclonal antibodies, cytokines and vaccines are available. The goal of our present work is to highlight some of the promising new and experimental local therapies of CLs.

**Hexadecylphosphocholine**

Hexadecylphosphocholine is an antineoplastic drug that inhibits tumour cell growth and might also exert immunoregulatory properties [7, 8].

Dummer et al. [9] treated 24 patients with 6% topical hexadecylphosphocholine (1 drop/10 cm² lesion) for 8 weeks. Fifteen suffered from mycosis fungoides (MF), 7 had CBCL and 2 had lymphomatoid papulosis. Of 15 CTCL patients, 12 were evaluable. Two complete remissions (CR), 4 partial remissions (PR) and 1 minor remission were observed. Of 7 CBCL patients, 6 were evaluable. One CR, 3 PR, 1 case of stable disease and 1 case of progressive disease were seen. Both patients with lymphomatoid papulosis had a CR. Histological evaluation demonstrated only a partial clearing of infiltrating lymphocytes in lesions that showed PR or CR clinically. Fifty-six percent of evaluable CL patients (10/18) achieved an objective response rate (PR and CR) [9].

**Table 1. WHO-EORTC classification of CLs**

| CTCL and cutaneous NK cell lymphomas | MF |
| MF variants and subtypes | Folliculotropism MF |
| | Pagetoid reticulosis |
| | Granulomatous slack skin |
| Sézary syndrome | Adult T-cell leukaemia/lymphoma |
| Primary cutaneous CD30+ lymphoproliferative disorders | Primary cutaneous anaplastic large-cell lymphoma |
| | Lymphomatoid papulosis |
| Subcutaneous panniculitis-like T-cell lymphoma | Extranodal NK/T-cell lymphoma, nasal type |
| | Primary peripheral CTCL, unspecified |
| | Primary aggressive epidermotropic CD8+ CTCL (provisional) |
| | γ/δ CTCL (provisional) |
| | Primary CD4+ small/medium-sized pleomorphic CTCL (provisional) |

| CBCL |
| Primary marginal zone CBCL |
| Primary cutaneous follicle centre lymphoma |
| Primary diffuse large CBCL, leg type |
| Primary diffuse large CBCL, other |
| Intravascular large B-cell lymphoma |

| Precursor haematological neoplasm |
| CD4+/CD56+ haematodermic neoplasm (blastic NK cell lymphoma) |

EORTC = European Organization for Research and Treatment of Cancer; NK = natural killer.

**Table 2. Classical topical treatment options in CL**

<table>
<thead>
<tr>
<th>Skin involvement</th>
<th>Topical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited/localized</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Nitrogen mustard</td>
</tr>
<tr>
<td></td>
<td>Carmustine</td>
</tr>
<tr>
<td></td>
<td>Local radiation</td>
</tr>
<tr>
<td></td>
<td>Topical retinoid (bexarotene)</td>
</tr>
<tr>
<td></td>
<td>Ultraviolet B</td>
</tr>
<tr>
<td></td>
<td>Psoralen + ultraviolet A</td>
</tr>
<tr>
<td>Generalized</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td></td>
<td>Carmustine</td>
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<tr>
<td></td>
<td>Ultraviolet B</td>
</tr>
<tr>
<td></td>
<td>Narrow-band ultraviolet B</td>
</tr>
<tr>
<td></td>
<td>Psoralen + ultraviolet A</td>
</tr>
<tr>
<td></td>
<td>Total skin electron beam therapy</td>
</tr>
</tbody>
</table>
Dumontet et al. [10] performed a phase II trial to evaluate 6% topical hexadecylphosphocholine solution (2 drops/10 cm² lesion) for the treatment of 12 CTCL patients. All patients had received at least 1 prior systemic or topical treatment. The study drug was administered for 8 weeks, once per day during the first week, then twice every day for 7 weeks. Five patients were considered to be in CR, 2 patients had PR and 5 patients had stable disease. The overall response rate was 58% with a median duration of response of 12 months. The main side effects were moderate to mild pruritus or desquamation in 57% and 50% of patients, respectively. No systemic or biological toxicity was observed [10]. These studies have shown that hexadecylphosphocholine is a safe, simple and effective treatment in both untreated and previously treated patients in early patch form CL (table 3).

Methotrexate

Methotrexate (MTX) competitively inhibits dihydrofolate reductase, therefore blocks DNA synthesis and prevents mitosis [11]. Oral or parenteral MTX is approved for the treatment of advanced MF; however, its systemic toxicity has precluded its use in patients with early-stage MF. Topical therapy of early-stage MF with the existing oral or parenteral MTX formulations is ineffective because of the inability of the drug to penetrate the stratum corneum from aqueous solutions [12]. For this reason, MTX-laurocapram was developed, which is a topical hydrophilic gel formulation of MTX (1% wt/wt) with the penetration enhancer laurocapram.

Demierre et al. [13] presented the results of a phase I/II study in 10 patients with early-stage MF who were treated topically with MTX-laurocapram. The gel formulation of the product was applied to the total body surface at daily doses of 12.5 or 25 g/m², excluding the genital, perianal areas, nipples, face and skin under the breasts, on an every-other-day basis for 24 consecutive weeks. Of 10 patients, 9 completed the study. At the end of the treatment phase (week 24), 3 patients (33%) had a moderate response, 4 (44%) had a slight response and 2 (22%) had no response to treatment. In summary, a total of 7 (78%) patients demonstrated a slight to moderate response to treatment. Adverse events consisted of local skin reactions of mild severity such as pruritus, rash, burning and dryness. No systemic reactions or clinically significant laboratory abnormalities were observed. Serum levels of MTX, as measured 24–48 h following the topical application, were under the lowest limit of detection in all samples analysed [13].

The results obtained in this study indicate that MTX-laurocapram is safe and well tolerated, and it seems that systemic exposure to the drug is not significant. Despite the relatively low number of patients, efficacy outcomes were positive.

Tazarotene

Retinoids, which are derivatives of vitamin A, modulate the differentiation and proliferation of keratinocytes and lymphocytes. Topical bexarotene in gel form is a synthetic retinoid-X-receptor-selective retinoid, which has

| Table 3. Therapeutic approaches for the treatment of CTCL and CBCL with the antineoplastic drug hexadecylphosphocholine |
|---|---|---|---|---|---|
| References | Patients enrolled | Patients evaluated | Treatment schedule | Clinical response | Histological clearance | Relapse |
| Dummer et al. [9] | 15 CTCL | 12 | 1st week 1 × /day, next 7 weeks 2 × /day, in PR or MR additional 4 weeks | 2 CR, 4 PR, 1 MR, 1 CR, 3 PR, 1 SD, 1 PD | yes in 5 CR patients, but no decrease in lymphocyte numbers in the deeper dermis | n.a. |
| | 7 CBCL | 6 |
| Dumontet et al. [10] | 12 CTCL | 12 | 1st week 1 × /day, next 7 weeks 2 × /day | 5 CR, 2 PR, 5 SD | n.a. | none until a median follow-up of 12 months in 2 CR + 1 PR patients; in 3 patients, none between 24 and 54 months |
| MR = Minor remission; SD = stable disease; PD = progressive disease; n.a. = not applicable. |

already been approved by the Food and Drug Administration (FDA) for the treatment of refractory IA and IB MF lesions. Tazarotene is a synthetic retinoid in a gel or cream formula, which binds to the retinoic acid receptor β- and γ-subtypes. As the latter is the dominant receptor in the skin, the selective binding capacity of tazarotene eliminates many side effects, which possibly occur when retinoic acid receptor subtypes are generally activated. The FDA has approved tazarotene for the treatment of psoriasis and acne vulgaris.

Apisarnthanarax et al. [14] conducted an open-label pilot study to assess the efficacy and tolerability of 0.1% tazarotene gel in the treatment of early patch or plaque MF lesions limited to less than 20% body surface area. Twenty patients were enrolled, 19 received treatment, and 16 completed at least 4 weeks of topical therapy. Eleven of 19 patients or 58% experienced at least moderate (>50%) global improvement in all index lesions, and 35% of 99 index lesions cleared completely. On the basis of grading of index lesions, mean significant differences were observed after treatment in plaque elevation, scaling and erythema. Only pruritus did not change significantly and remained stable. Of 19 patients, 16 (84%) experienced mild or moderate local skin irritation manifested by peeling, erythema, burning and tenderness that was managed successfully with topical steroids or by reducing the frequency of treatment. Histological evaluations showed reductions in lymphocytic infiltrates and percentage of CD45RO+ lymphocytes, and increases in the percentage of CD8+ lymphocytes during the therapy course.

The rate of irritation was similar or slightly higher than that reported with topical bexarotene gel for MF lesions, but the pilot study with tazarotene included few patients, was non-randomized, had no vehicle control and was susceptible to bias in lesion assessments [14]. Nonetheless, these data suggest that tazarotene 0.1% gel combined with topical corticosteroids may be an effective adjuvant therapy for refractory MF lesions.

**Imiquimod**

Imiquimod is a topical Toll-like receptor (TLR)-7 and TLR-8 agonist constitutively activating the transcription factor NF-κB, therefore inducing the production of pro-inflammatory cytokines and chemokines including IFN-α, IFN-γ, interleukin-12 and tumour necrosis factor-α. This results in activation of antigen-presenting cells and the mounting of a profound T-helper 1 (Th1) antitumoural cellular immune response [15]. The pro-inflammatory activity of imiquimod can also be correlated with adenosine receptor signalling pathways and receptor-independent reduction of adenylyl cyclase activity [16]. At higher concentrations, imiquimod exerts a pro-apoptotic activity, which is dependent on bcl-2 proteins and involves caspase activation [16]. The cream formulation has been approved for the treatment of external genital and perianal warts, actinic keratoses and primary superficial basal cell carcinoma. As CTCL is dominated by T-helper 2 cytokines, the enhancement of Th1 immune responses has a therapeutic role. So far several case reports and a few pilot studies exist, showing the efficacy of imiquimod in patients with different forms of CTCL such as MF [17–27], CD30+ anaplastic large-cell lymphoma [20, 23, 28], primary cutaneous follicle centre lymphoma [29] and primary CBCLs [23, 25].

In a series of 6 CTCL patients, Deeths et al. [21] observed 50% clinical and histological clearing and a significant improvement in clinical scores. Coors et al. [23] observed CR in more than 50% of their CTCL patients, and additionally they observed a PR in 2 out of 3 CBCL patients; however, the effect of imiquimod seemed to be less potent in CBCL.

Generally, treatment frequencies ranged from once daily to once weekly applications. Time to response was already reached after 2 weeks in some patients, and the duration of remission was between 5 and 45 months.

Previous studies of Urosevic et al. [30] showed that the clinical inflammatory reaction in response to imiquimod was correlated with the IFN-α gene signature and with the number of plasmacytoid dendritic cells in treated lesions, showing that these may have a role in the clinical response to imiquimod.

Imiquimod treatment was generally well tolerated; local irritation and erythema were common, but pruritus, burning, pain, tenderness, infections, ulceration and postinflammatory discolouration occurred in some patients [31]. Severe reactions usually developed in patients on an intensive regimen, which usually resolved within 1–2 days after cessation and could be avoided by less frequent applications [17]. Although absorption into the circulation is less than 1%, in rare cases systemic side effects were observed such as fatigue, fever, myalgia, nervous system impairment and gastro-intestinal symptoms [32].

The case reports cited above and pilot studies demonstrated that imiquimod might be effective in some cases with therapy-resistant lesions of CTCL as well as of CBCL with an acceptable safety profile (table 4).
Intramuscular recombinant IFN-\(\gamma\) has been investigated for the immunotherapy of CTCL with promising response rates, although severe toxicity was seen [34]. Intratumoural delivery of recombinant IFN-\(\gamma\) has been attempted to overcome systemic side effects [35]; however, the short half-life of the cytokine was a complicating factor.

TG-1042 is a replication-deficient adenovirus vector expressing IFN-\(\gamma\) to target CTCL lesions [36]. Intralésional injection produces sustained local IFN-\(\gamma\) protein levels while systemic IFN-\(\gamma\) levels remain low.

In a phase I/II study, all 5 evaluable CBCL patients presented with a local response (3 CR and 2 PR), and 45% of the 29 evaluable CTCL patients responded to TG-1042 treatment (7 CR and 6 PR). Out of the total 18 patients with objective local response, 15 showed systemic response with the additional clearance of non-injected skin lesions (7 CR and 8 PR in non-treated tumours). CTCL subtypes, such as MF, Sézary syndrome and CD30+ anaplastic large-cell lymphoma, showed different response rates to TG-1042 injections. Clinical response was seen in 8 out of 20 MF patients, but patients with Sézary syndrome did not benefit from treatment. All 3 evaluable patients with CD30+ anaplastic large-cell lymphoma responded with a CR in the treated lesions. It seems that more localized lesions in earlier stages of the disease in conjunction with CD30 expression respond better to treatment. In general, CBCL lesions are easily accessible.
for treatment and responded very well to TG-1042; therefore, a larger multicentre phase II study currently evaluates the response rates in different CBCL subtypes [37].

Based on a recent work of Urosevic et al. [38], it appears that both the expression of the transgene and the adenoviral vector itself contribute to the regression of skin lesions. Gene expression profiles of skin lesions obtained from CL patients before and after treatment with TG-1042 revealed a distinct gene signature consisting of IFN-γ- and numerous IFN-α-inducible genes. IFN-γ very likely promotes the immunogenicity of the tumour, while type I IFNs, on the other hand, exhibit profound antitumoural effects by acting on host immune cells [38].

Treatment with TG-1042 was well tolerated, usually with grade 1 or 2 adverse events such as injection site reactions, flu-like syndrome, fatigue and possibly dose-dependent headache. Unspecified colitis, vomiting following vasovagal syncope and transient fever were reported as possibly related side effects.

This therapy induced regression in CTCL and CBCL patients both at the injection site and systemically with tolerable side effects (table 5).

**Rituximab**

Tumoural pre-B and mature B cells express the CD20 antigen, which can be targeted by rituximab, a human-mouse chimeric monoclonal antibody. Rituximab kills CD20+ tumour cells by directly inducing apoptosis, by triggering complement-mediated lysis and by antibody-dependent cell-mediated cytotoxicity [39, 40].

Nodal B-cell lymphoma can be successfully treated with intravenous rituximab infusion as monotherapy or in combination with other agents [41–43].

Heinzerling et al. [44] reported for the first time the use of intralesional rituximab in 2 patients with primary CBCL. One patient had progressive nodular lesions on the scalp and on the face. The other patient presented with recurrence of tumour nodules in different body parts. Rituximab was injected 3 times a week, each time 30 mg, followed by a 3-week treatment-free period. An inflammatory response in the injected lesions was observed approximately 2–3 h after each injection and lasted for a few hours. After 6–9 injections, some of the nodules flattened and diminished in size, and others, including some that were not treated, had completely resolved. No adverse effects occurred except pain during or shortly after injection and, in 1 patient, a slight rise in body temperature. Due to the treatment, a prolonged complete disappearance of B cells from peripheral blood samples was observed [44].

Later on Kerl et al. [45] treated 8 primary CBCL patients with rituximab. Patients selected for treatment had follicle centre (4 patients) and marginal zone (4 patients) lymphoma. These are the most frequent CBCL entities, which have an indolent course and rarely disseminate to internal organs, but their incidence of recurrence is high [5, 46]. Six patients received intralesionally 10–30 mg rituximab, 3 times weekly for 1 or 2 cycles with a 4-week interval. Two patients were treated with intravenous rituximab and received 375 mg/m², once weekly for 4 consecutive weeks. All patients reached CR, and the 2 patients treated intravenously did not relapse during a follow-up period of 18–24 months. Four of 6 patients treated intralesionally presented a relapse of new lesions at another site within a mean of 6 months after treatment. However, the injected lesions did not recur. New lesions also responded to another cycle of intralesional rituximab [45].

Intralesional rituximab therapy was well tolerated without severe side effects. All patients reported moderate pain during the injection procedure. On the other hand, no burning or erythema was reported.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients enrolled</th>
<th>Patients evaluated</th>
<th>Treatment schedule</th>
<th>Local response</th>
<th>Global response</th>
<th>Histological clearance</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urosevic [37]</td>
<td>32 CTCL</td>
<td>29</td>
<td>$3 \times 10^{11}$ TVP TG-1042 i.t. for up to 4 cycles</td>
<td>7 CR, 6 PR</td>
<td>3 CR, 2 PR</td>
<td>15</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

TVP = Total viral particles; i.t. = intratumourally; n.s. = not stated.
It seems that this treatment has a potential advantage when lesions are localized at sites that are difficult to treat with radiotherapy or surgery and when secondary scarring or alopecia is expected to occur. In summary intralesional rituximab is a valuable alternative option for the treatment of CBCL, but the risk of relapse was relatively high (table 6).

**Photodynamic Therapy**

Photodynamic therapy (PDT) requires the presence of a photosensitizer, light and oxygen. In dermatology, 5-aminolevulinic acid (5-ALA) and the methyl ester of 5-ALA are the most commonly used photosensitizers, which may semiselectively accumulate in abnormal skin tissue and are converted to protoporphyrin IX, inducing a photochemical and phototoxic skin reaction through reactive oxygen radicals in the presence of visible light [47, 48]. Following serial evaluations immunological effects have been additionally described.

Boehncke et al. showed that the photosensitizer is mainly taken up by the lymphocytes in CL plaques [49] and that PDT has the capability to inhibit proliferation of transformed T cells [50].

Orenstein et al. [51] observed that malignant cells in CTCL plaques have a greater ability to convert ALA into protoporphyrin IX than peripheral blood lymphocytes. The observations of Rittenhouse-Diakun et al. [52] might explain the greater susceptibility of malignant lymphocytes to photosensitizers. They found that activated lymphocytes express higher levels of CD71 (transferrin receptor), making them able to take up more iron and, therefore, produce more protoporphyrin IX.

Based on several existing reports [51, 53–68], it can be concluded that PDT treatment of CTCL lesions is of benefit in most (CR in more than 86% of cases presented in table 7) but not all patients. The numbers of treatments to reach CR were usually between 1 and 12, and remission periods were between 3 and 106 months (table 7). Lesions in remission had a peculiar histological appearance, since atypical lymphocytes continued to be present in the dermis.

A recent study performed by Mori et al. [69] used ALA-PDT and red light at the standard dose used for basal cell carcinoma to treat 3 patients with single early CBCL lesions. They reported CR following a single session in all of the patients, with a follow-up of between 8 and 17 months.

PDT therapy was tolerated well; in most cases erythema, oedema, postinflammatory hyperpigmentation, local discomfort, burning and pain were reported. In rare cases, superficial blisters, erosion and ulceration occurred.

Based on small studies with few patients and numerous case reports, it seems that CL patients with localized lesions can benefit most from PDT. It is very likely that lymphocytes in the plaque are only inactivated but not eliminated and remission periods are highly variable, therefore a regular follow-up is necessary.

Further studies will be necessary to evaluate whether the combination with other therapeutic modalities enhances efficacy. Umegaki et al. [64] have already reported a case of cutaneous anaplastic large-cell lymphoma, which was effectively treated by PDT prior to radiotherapy.

**308-nm Excimer Laser**

UVB phototherapy has been used for treating various skin diseases including CL. Different CL forms respond well to either broad-band or narrow-band UVB photo-

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**Table 6. Therapeutic approaches for the treatment of CBCL with the human-mouse chimeric monoclonal antibody rituximab**

<table>
<thead>
<tr>
<th>References</th>
<th>Patients enrolled</th>
<th>Treatment schedule</th>
<th>Time to response</th>
<th>Clinical response</th>
<th>Histological response</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinzerling et al. [44]</td>
<td>2</td>
<td>30 mg i.l. 3 ×/week, 1 week treatment, 3-week treatment-free period</td>
<td>6–9 injections</td>
<td>CR, PR (numbers n.s.)</td>
<td>no (only 2 lesions assessed)</td>
<td>in 12 months 1 new lesion, otherwise n.s.</td>
</tr>
<tr>
<td>Kerl et al. [45]</td>
<td>6</td>
<td>10–30 mg i.l. 3 ×/week for 1 or 2 cycles with a 4-week interval</td>
<td>CR after 1 or 2 cycles</td>
<td>6 CR</td>
<td>n.s.</td>
<td>4 patients in 4–8 months</td>
</tr>
</tbody>
</table>

i.l. = Intralesionally; n.s. = not stated.
therapy. Recently, it has been reported that a 308-nm xenon chloride (XeCl) UVB laser is highly effective for treating psoriasis [70], and, over the past few years, several excimer laser studies have been published for the treatment of early-stage MF.

It seems that effective induction of T-cell apoptosis is responsible for the greater clinical efficacy of XeCl laser compared to other UVB sources [71, 72].

Nistico et al. [73] treated 5 patients with a total of 10 lesions with a clinical and histological diagnosis of primary CL with repeated applications of the XeCl laser, until CR was achieved or up to a maximum of 10 applications. The cumulative UVB dose was between 6 and 12 J/cm². After a 1-year follow-up, all patients were in CR [73].

Passeron et al. [74] treated 5 patients with patch-stage or plaque-stage primary CL in a XeCl laser study. The 50 mJ/cm² initial fluences were increased by 100 mJ/cm² every 2 sessions. Treatment was administered twice weekly until clinical clearance or minimal residual activity was achieved. A CR was obtained for 4 of the 5 patients, and minimal residual activity (PR) was observed in the fifth. Clinical healing was obtained in 11–21 sessions, with a cumulative dose ranging from 2.4 to 16.1 J/cm². No clinical recurrence was noted 3 months after the end of the sessions.

Later the same group conducted a XeCl laser trial with 10 MF patients. A total of 29 lesions were treated as described in their previous study. The mean cumulative dose ranged from 1.3 to 16.1 J/cm². After treatment sessions, 25 CR and 3 PR were observed, and 1 lesion did not respond. Follow-up was performed in 19 lesions for a median period of 8–26 months; 13 persistent CR, 3 continued PR and in 2 cases relapses were observed, and 1 lesion remained non-responsive. Histology was consistent with clinical results, except for 1 case with persistence of a few mycosis cells in the epidermis despite a clinical appearance of healing [75].

Afterwards this treatment option was studied in lymphomatoid papulosis [76] and CD30+ cutaneous lymphoproliferative disorders [77].

Side effects were manageable; usually slight erythema, pruritic sensation and transient hyperpigmentation were noticed in all patients, with spontaneous resolution. In the case of intense erythema, the sessions were cancelled and the fluence at the next treatment corresponded to the highest dose that did not induce adverse effects.

Table 8 briefly summarizes the results obtained with the 308-nm excimer laser for various CL forms and lymphomatoid papulosis.
Conclusions and Future Perspectives

Skin-directed therapies using topical formulations are preferred for the majority of patients with early-stage CL, which usually include topical corticosteroids, topical chemotherapeutic agents, the topical retinoid bexarotene, electron beam therapy and phototherapy. Not all patients respond to these therapies, and some of them become refractory to treatment [78]. In this field there are interesting developments, but there are often insufficient data to compare the efficacy and side effects of available and possible future therapies.

The topical administration of antineoplastic agents such as MTX is very likely restricted by the poor diffusion of the drug across the stratum corneum. Therefore attempts have been made to increase transdermal transport through electroporation [79, 80] and using an erbium:YAG laser in animal models. Both techniques significantly enhanced the permeation of MTX. The enhancing effect was more pronounced after applying the laser. Electroporation treatment resulted in a twofold increase in MTX flux, laser pretreatment produced a 3- to 80-fold enhancement and combination of laser and electroporation pretreatment resulted in a higher drug permeation than either technique alone [80].

Retinoids have been used for years as monotherapy and in combination for CTCL treatment. Retinoids have been available since the approval of oral bexarotene for CTCL. Topical retinoids and rexinoids, especially the selective ones, have fewer side effects than the oral ones; therefore, the use of retinoids and rexinoids will require strategies to identify novel receptor-selective subtypes with a better therapeutic index to decrease the possible side effects.

Restoring Th1 immunity in CL is an important therapeutic approach, therefore the role of IFNs (IFN-α and in recent years IFN-γ) and immunomodulators, which are potent IFN inducers, is becoming more important. Imiquimod (TLR-7 and TLR-8 agonist), a potent IFN-α inducer, has been reported to be beneficial for some patients with localized stage IA MF, and agents other than imiquimod are also under investigation. Recent data showed that EAPB0203, a member of the imidazoquinoxaline family, may have a future therapeutic role in the treatment of HTLV-I-negative peripheral T-cell lymphoma [81], and it has also been shown that the novel tellurium immunomodulator AS101 induces a dose-dependent G2/M arrest in CTCL cell lines and delays tumour growth in mice, when injected intratumourally [82, 83]. Formerly it was shown that a replication-deficient adenovirus, which carries the IFN-γ gene, has a therapeutic effect for the treatment of CL. A phase I/II clinical trial in CTCL and CBCL patients was recently completed, and clinical studies are still ongoing in CBCL patients [36, 37].

The oligonucleotide CpG-7909, which is a TLR-9 agonist, has shown promising results in CTCL patients [84], and a phase I/II study has been initiated to investigate CpG-7909 together with radiation therapy in low-grade B-cell lymphoma or MF patients.

Antibodies against antigens on the surface of lymphoma cells have an emerging therapeutic role. CD20 is

<table>
<thead>
<tr>
<th>References</th>
<th>Patients enrolled</th>
<th>Number of lesions</th>
<th>Sessions</th>
<th>Cumulative UVB dose, J/cm²</th>
<th>Clinical response</th>
<th>Histological clearance</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nistico et al. [73]</td>
<td>5</td>
<td>10</td>
<td>4–10</td>
<td>6–12</td>
<td>10 CR</td>
<td>yes</td>
<td>none in 12 months</td>
</tr>
<tr>
<td>Passeron et al. [74]</td>
<td>5</td>
<td>5</td>
<td>11–21</td>
<td>2.4–16.1</td>
<td>4 CR, 1 MR</td>
<td>yes in 3 patients without atypical cells</td>
<td>none in 3 months</td>
</tr>
<tr>
<td>Passeron et al. [75]</td>
<td>10</td>
<td>29</td>
<td>6–46</td>
<td>1.3–16.1</td>
<td>25 CR, 3 PR, 1 NR</td>
<td>yes, consistent with clinical response</td>
<td>none in 8–26 months, 19 lesions</td>
</tr>
<tr>
<td>Kontos et al. [76]</td>
<td>3</td>
<td>multiple</td>
<td>13–22</td>
<td>0.4–0.5</td>
<td>patient 1: 75% CR; patient 2: 100% CR; patient 3: NR</td>
<td>patient 1: n.a.; patient 2: yes; patient 3: n.a.</td>
<td>in patient 2, none in 13 months</td>
</tr>
</tbody>
</table>

MR = Minor remission; NR = no response; n.a. = not applicable.
† Patient 1 had lymphomatoid papulosis, patient 2 and 3 had MF.
strongly expressed on the surface of malignant B cells and can be targeted by rituximab [39, 40]. In the case of primary CBCLs, intralesional therapy with rituximab has already been found to be effective [44, 45]. In comparison with intravenous administration, intralesional application of the drug allows the use of lower doses and fewer side effects. Recently a clinical study has been designed to investigate the antitumour activity of rituximab combined with CpG-7909 in patients with relapsed/refractory CD20+ B-cell non-Hodgkin’s lymphoma [85]. Objective responses occurred in 24% of patients overall and in 50% of patients who after combination therapy received CpG-7909 alone for an additional 20 weeks; this cohort included 2 patients with rituximab-refractory disease. Most common adverse events were mild to moderate systemic flu-like symptoms, injection site reactions and neutropenia [85]. Based on these results, it would be reasonable to check this combination therapy in primary CBCL patients.

Phototherapy has been utilized for decades in the treatment of CL and recently it has been shown that PDT is also an effective, non-invasive and safe therapeutic approach [86]. Reports already exist, which suggest that this therapeutic modality can be effectively used prior to radiotherapy [64]. Treatment of ALA-PDT with PUVA represents a promising option as it was shown that this combination inhibits the proliferation of a lymphoma cell line in vitro [87].

The XeCl laser is a new and very useful form of UVB phototherapy. During XeCl laser therapy, the overall treatment time is shorter, the treatments are less frequent and the cumulative UV dose is significantly lower than those used in standard UV phototherapies; therefore, it is presumed that the lower therapeutic cumulative dose of the XeCl laser involves a lower risk of carcinogenesis. It is considered that longer-wavelength UVB phototherapy would be ideal for the treatment of thick skin lesions, while short-wavelength UVB radiation would be optimal for the treatment of thin ones. To further optimize treatment results, the surface of skin lesions can be moistened to enhance the penetration of radiation. As with other UV therapies, combination therapy seems to be the next step to improve efficacy [88].

Arsenic compounds such as As$_2$O$_3$ have been shown to induce cell death by the inhibition of bcl-2. In acute promyelocytic leukaemia, this treatment modality led to CR in 90% of the patients [89–91]. In patients with Sézary syndrome, this kind of therapy has not been successful as As$_2$O$_3$ levels were low in the skin [92]. Tun-Kyi et al. [93] have shown that As$_2$O$_3$ induced apoptosis of CTCL cells by down-regulating transcription factors that stimulate the expression of anti-apoptotic genes. Local injection of As$_2$O$_3$ induced tumour regression in MF tumour-bearing mice [93]. These results demonstrate that As$_2$O$_3$ could be a novel local treatment option for CTCL.

In summary, ongoing and future standardized clinical trials will hopefully provide new data regarding experimental skin-directed treatment options for CL patients. As with other already well-established treatment options, combination therapy seems to be a logical future step to improve efficacy.

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References

Skin-Directed Treatment of Cutaneous Lymphomas


