Research Advances in Topical and Physical Therapies for Cutaneous T-cell Lymphoma (Postprint)

Authors: Wang Shiqi, Chi Cheng, Liu Jie

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Abstract

Cutaneous T cell lymphoma (CTCL) is predominantly classified as indolent lymphoma with slow disease progression, and patients are often diagnosed at early disease stages. Topical medications and physical therapies play an important role in CTCL treatment, including topical corticosteroids, immunosuppressants, retinoids, radiotherapy, and phototherapy. In recent years, studies have re-evaluated the efficacy and safety of traditional topical medications and physical therapy methods for CTCL. Concurrently, novel topical medication and physical treatment strategies for CTCL have continued to emerge, such as topical azarotene, resiquimod, photochemotherapy combining UVA with novel photosensitizers, and photodynamic therapy. This article provides a review of research progress on topical medications and physical therapies for CTCL.

Full Text

Preamble

Advancements in Local Medication and Physical Therapy for Cutaneous T-Cell Lymphoma

Wang Shiqi, Chi Cheng, Liu Jie

Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Liu Jie, E-mail: Liujie04672@pumch.cn

Abstract

Cutaneous T-cell lymphoma (CTCL) predominantly represents an indolent lymphoma with slow disease progression, and most patients are diagnosed at an early stage. Local medication and physical therapy play a crucial role in CTCL treatment, encompassing topical corticosteroids, immunosuppressants, retinoids, radiotherapy, and phototherapy. In recent years, studies have re-evaluated the efficacy and safety of traditional local and physical therapeutic approaches for CTCL. Concurrently, novel strategies have emerged, including topical tazarotene and resiquimod, UVA combined with new photosensitizers in photochemotherapy, and photodynamic therapy. This article reviews recent research progress in local medication and physical therapy for CTCL.

Keywords

cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome; skin-directed therapy; physical therapy

Cutaneous T-cell lymphoma (CTCL) comprises a group of T-cell lymphomas primarily affecting the skin, with potential involvement of lymph nodes, bone marrow, and visceral organs. Mycosis fungoides (MF) and Sézary syndrome (SS) represent the two most common CTCL subtypes. Patients with early-stage localized disease typically receive local medication or physical therapy, while those with advanced refractory disease require systemic or combination therapy. Consequently, local medication and physical therapy occupy a pivotal position in CTCL management. Recent advances in understanding CTCL pathogenesis and improvements in oncologic treatment technologies have yielded significant therapeutic breakthroughs. While numerous publications have reported on systemic therapy for CTCL, particularly targeted therapies, few have addressed developments in local treatment modalities. This review summarizes the current status and research progress of local medication and physical therapy for CTCL.

1. Advances in Topical Medications for CTCL

Topical corticosteroids, immunosuppressants (nitrogen mustard, carmustine), and retinoids have been used to treat CTCL for decades. Recent studies have re-evaluated their efficacy and safety, while identifying promising new agents such as tazarotene and resiquimod for early-stage MF.

1.1 Topical Corticosteroids

Topical corticosteroids have been used for CTCL since the 1960s, exerting both anti-inflammatory and anti-proliferative effects. Their effectiveness is widely recognized. Zackheim et al. followed approximately 200 patients, reporting that 94% of stage T1 patients and 82% of stage T2 patients achieved partial remission (PR) or complete remission (CR). Additionally, intralesional corticosteroid

injection successfully treated localized lesions in four MF patients resistant to conventional therapies, including tumor-stage and CD30+ large cell transformation MF, yielding satisfactory outcomes.

1.2.1 Nitrogen Mustard

Nitrogen mustard is an alkylating agent that treats MF by inhibiting tumor cell proliferation and disrupting interactions between keratinocytes, Langerhans cells, and T cells. Its aqueous solution and ointment formulations have been used since the 1950s, though both carry high rates of allergic contact dermatitis. In 2013, Lessin et al. conducted a multicenter, randomized, single-blind trial of 260 stage IA-IIA MF patients treated with 0.02% nitrogen mustard gel or ointment for two years. Response rates were 59% and 48%, respectively, with the gel demonstrating faster onset ($p<0.012$). No systemic absorption or severe adverse events were detected. The gel formulation dries easily and offers convenient application, receiving approval for stage IA and IB MF treatment. Despite widespread successful use, concerns persist regarding increased risks of second malignancies and chronic pulmonary disease. However, Lindahl et al. conducted a 30-year population-based cohort study comparing 110 MF patients treated with topical nitrogen mustard versus 193 untreated patients, finding no significant differences in second cancer incidence (including melanoma, non-melanoma skin cancer, and lung cancer), other complications (such as chronic pulmonary disease), or mortality risk, thereby confirming the safety of topical nitrogen mustard therapy.

1.2.2 Carmustine

Carmustine is another topical alkylating agent for MF, with recent research focusing on combination therapy. CTCL tumor cells may evade carmustine' s cytotoxic effects through O6-alkylguanine DNA alkyltransferase (AGT), a DNA repair enzyme. Apisarnthanarax et al. demonstrated that O6-benzylguanine significantly reduces AGT levels in CTCL lesions, and its combination with carmustine enhances efficacy while reducing dosage and adverse effects. Topical carmustine monotherapy or combined with systemic interferon- , interferon- , or isotretinoin effectively treats folliculotropic MF, likely due to its superior penetration compared to nitrogen mustard. Heisig et al. reported successful treatment of folliculotropic MF with topical cytarabine combined with carmustine. Local carmustine therapy exhibits minimal side effects, primarily erythema, telangiectasia, and hyperpigmentation.

1.3 Topical Retinoids

Retinoids, vitamin A derivatives, treat CTCL through anti-proliferative, pro-apoptotic, and immunomodulatory mechanisms mediated by retinoic acid receptors (RAR) and retinoid X receptors (RXR). Bexarotene, which selectively binds RXR, remains the only retinoid approved by the US Food and Drug Administration (FDA) for topical CTCL treatment.

Apisarnthanarax et al. found 0.1% tazarotene effective for refractory MF. Compared to bexarotene, tazarotene exhibits stronger affinity for RAR, particularly RAR- , and offers greater accessibility and cost-effectiveness. A prospective study of 0.1% tazarotene monotherapy in 10 stage IA-IIA CTCL patients for six months demonstrated 60% CR, with 83% of CRs lasting over six months. No disease progression occurred during treatment or follow-up, and side effects were limited to pruritus, burning sensation, and erythema without severe adverse events.

Alitretinoin represents the only topical retinoid with dual RAR and RXR activity. Oral alitretinoin successfully treats MF, and its topical formulation effectively manages refractory CTCL lesions.

1.4 Novel Topical Agents

Despite symptom improvement with conventional therapies, refractory cases remain challenging, and relapse after discontinuation is common. Imiquimod, a Toll-like receptor 7 (TLR7) agonist, promotes production of interferon- , tumor necrosis factor- , and interleukin-12. It effectively treats early-stage MF and can achieve complete clearance of lesions in folliculotropic and tumor-stage MF.

Resiquimod activates both TLR7 and TLR8. While TLR7 is expressed only in plasmacytoid dendritic cells, TLR8 is present in all myeloid-derived dendritic cells, which dominate both normal and inflammatory skin. Therefore, resiquimod theoretically offers broader activity than imiquimod. Its mechanism in MF involves eliminating malignant clones, promoting benign T-cell clone proliferation, and enhancing skin T-cell cytokine and natural killer cell function. In a Phase I clinical trial, 0.03% and 0.06% resiquimod gel applied to 12 stage IA-IIA refractory MF patients yielded 75% clinical response and 30% complete lesion clearance. Notably, resiquimod induced remission in non-treated lesions —a unique finding among all topical CTCL agents. Side effects are minimal, primarily limited to local skin irritation.

2. Advances in Phototherapy for CTCL

Phototherapy employs ultraviolet A (UVA), ultraviolet B (UVB), or psoralen plus UVA (PUVA). UVB includes broad-band (BB-UVB, 290-320 nm) and narrow-band (NB-UVB, 311-312 nm). UVA comprises UVA1 (340-400 nm) and UVA2 (320-340 nm). Recent retrospective studies of NB-UVB and PUVA for MF revealed that NB-UVB' s short-term side effects include erythema, pruritus, lesion exacerbation, photosensitivity, vitiligo-like lesions, and freckling (lighter-colored, rounder, and more sharply demarcated than PUVA-induced freckles), plus elevated serum vitamin D levels. Long-term adverse effects include photocarcinogenicity and ocular effects (conjunctivitis, keratitis). PUVA side effects primarily involve lesion exacerbation, psoralen-related nausea, abdominal pain, fatigue, headache, and nail changes (subungual hemorrhage, photo-onycholysis, melanonychia). Long-term risks include pigmentary changes, photoaging (wrin-

kling, telangiectasia), cataracts, hypertrichosis, and skin tumors (non-melanoma skin cancers such as squamous cell carcinoma and basal cell carcinoma), though melanoma risk remains controversial. NB-UVB is generally preferred clinically as it can be safely used in pregnant women and children, with some recommending it as first-line therapy for pediatric early-stage MF.

PUVA serves as a first-line treatment for CTCL, demonstrating ideal efficacy in early-stage, recurrent, and folliculotropic MF. A retrospective trial investigating localized PUVA for refractory MF lesions in 10 patients reported complete response in six cases, partial response in three cases, and an overall response rate of 90.0%. However, some patients remain insensitive to psoralen plus UVA therapy. Recent research shows that small-molecule inhibitors of Ataxia Telangiectasia and Rad3-related kinase (ATR)—VE-821, VE-822, or Chir-124—combined with UVA can induce apoptosis through dual mechanisms of ATR enzyme inhibition and enhanced UVA photosensitivity, significantly increasing lymphocyte sensitivity to UVA.

However, PUVA carries oral psoralen-related side effects and long-term carcinogenic risks, while NB-UVB' s shallow penetration depth may lead to treatment failure and recurrence. UVA-1 penetrates deeper, reaching the reticular dermis and subcutaneous tissue, inducing apoptosis of infiltrating T cells and proving effective for early-stage CTCL. Olek-Hrab et al. treated four early-stage MF patients with UVA-1, achieving complete clinical and histopathological remission without adverse events. Kenan Aydogan et al. treated 19 early-stage MF patients with low-dose UVA-1 (20 J/cm² or 30 J/cm²), achieving CR in 11 patients (57.9%) and PR in three (15.8%). The mean cumulative dose was 1665 J/cm² (range 860-3120 J/cm²) with an average of 73 treatment sessions (43-107). Only two patients developed reversible hyperpigmentation without severe adverse events. Flow cytometry analysis of peripheral blood mononuclear cells showed no significant differences in CD3+, CD4+, CD7+, or CD8+ expression before and after treatment, suggesting no systemic side effects. Additionally, broad-band UVA (BB-UVA, 20 J/cm²), comprising 80.1% UVA1, effectively treats early-stage MF (response rate 33% vs. 13.3% for PUVA), particularly suitable for patients with oral psoralen contraindications or those unsuitable for UVA1, especially in darker skin types that tolerate 20 J/cm² BB-UVA without toxicity. BB-UVA also offers greater cost-effectiveness than UVA-1.

Another phototherapy advancement involves the 308 nm excimer laser, which provides targeted treatment with minimal damage to surrounding normal tissue. Compared to conventional phototherapy, it allows higher UVB doses and shorter treatment durations, achieving 66% response rates in localized MF and serving as an option for lesions in special locations (face, axilla, groin, or gluteal cleft).

3. Advances in Radiotherapy for CTCL

Radiation therapy (RT), including local RT and total skin electron beam therapy (TSEBT), represents one of the most effective CTCL treatments. Lympho-

cytes are the most radiosensitive cells. Local RT for early-stage MF achieves CR rates of 95-100%, typically requiring 1-2 treatment courses. Thomas et al. treated 58 MF patients (21 patch/plaque-stage, 34 tumor-stage, 3 erythrodermic) with single-fraction local RT, achieving 94% CR. Local RT has also successfully treated isolated ulcerated tumor-stage MF lesions on the vulva. TSEBT effectively treats generalized early-stage, advanced, tumor-stage, and erythrodermic MF. TSEBT can be administered before autologous or allogeneic hematopoietic stem cell transplantation to alleviate skin symptoms and potentially reduce post-transplant graft-versus-host disease. While previous reports described TSEBT combined with subcutaneous interferon as ineffective, further investigation revealed that TSEBT plus interferon achieved higher CR rates than TSEBT alone (63% vs. 36%), though without statistical significance. However, TSEBT requires lengthy treatment (6-10 weeks) and carries higher acute toxicity rates (erythema, blistering, hyperpigmentation, pain) than local RT, plus risks of alopecia, dystrophic nails, hypohidrosis, xerosis, cataracts, and second skin malignancies. Clinical use is recommended only for diffuse MF refractory to other therapies or for thick plaques and tumor-stage lesions.

4. Advances in Photodynamic Therapy for CTCL

Since the first successful treatment of MF with aminolevulinic acid-photodynamic therapy (ALA-PDT) in 1994, PDT research for MF has intensified. Advantages include excellent cosmetic outcomes (especially for facial and cervical lesions), selectivity, repeatability, low risk of toxicity accumulation, and minimal photosensitivity and carcinogenicity. PDT treats refractory MF and can be used on sensitive areas like the face and neck. For tumor-stage CTCL lesions, intradermal ALA injection followed by visible light irradiation (380-810 nm) after two hours can induce black necrotic changes within five days, indicating treatment efficacy.

Methyl-aminolevulinate (MAL), a novel photosensitizer, offers greater lipophilicity, penetration, shorter induction time, and higher selectivity than ALA. MAL-PDT successfully treats tumor-stage MF. Rivetti et al. successfully treated refractory, recurrent MF with MAL-PDT, suggesting PDT for MF plaques complicated by Bowen' s disease or actinic keratosis.

In summary, recent years have witnessed re-evaluation of traditional topical and physical therapies for CTCL alongside the emergence of novel local treatment strategies. However, the efficacy, safety, and optimal regimens of these modalities require further investigation through large-scale clinical trials. Additionally, deeper understanding of CTCL pathogenesis will drive exploration of innovative treatments to enhance efficacy and reduce adverse effects.

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Note: Figure translations are in progress. See original paper for figures.