

# Phototherapy and mycosis fungoides: what's new?

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## Abstract

The most common cutaneous T-cell lymphoma, mycosis fungoides (MF), is clinically characterized by erythematous-violaceous nodules and erythematous-scaly patches. In the early stages of MF, phototherapy is currently the first line of treatment and plays a significant role. This study aims to review and analyze the various phototherapy options for cutaneous lymphoma.

## Introduction

Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma (CTCL), is a low-grade lymphoma which originates from the peripheral epidermotropic T-cells. Clinically, it is characterized by the development of single or multiple erythematous-scaly patches and papules and erythematous-violaceous nodules of variable diameters, typically distributed in non-sun-exposed areas.<sup>1</sup> The etiology of CTCL is not completely understood, but

the role of some factors such as genetic abnormalities, environmental exposure, infectious agents and immune dysfunction has been supposed.<sup>1</sup> The interaction between the immune system and cutaneous cells may play a role in pathogenesis of CTCL and can be critically involved in supporting the progression of MF.<sup>2</sup> In fact, microenvironment cells may interact with tumor cells to gain a specific phenotype and their changes may recruit immunosuppressive cells. While in early-stage MF, reactive T-helper (Th) 1 and CD8+ T-lymphocytes contribute to the antitumor protection, in advanced phases, variations in tumor microenvironment from a Th1 to a Th2 response can encourage tumor growth and immune escape.<sup>3,4</sup> Hence, drugs stimulating the anti-tumor response (e.g., interferon- $\alpha$ ) and treatment with immune-modulating effects (e.g., phototherapy) have a well-known role in the management of CTCLs. Ultraviolet light (UVL) has been one of the most important treatment of MF in the last 50 years, with antiproliferative, photoimmunological, and immune-modulating effects. Treatments have traditionally included broadband, narrowband ultraviolet B light (nbUVB) and psoralen plus ultraviolet A light photochemotherapy (PUVA), but more recently UVA1 and excimer laser treatments are described. Nowadays, phototherapy is recommended for the first-line treatment of MF stages IA, IB and IIA, in particular nbUVB and PUVA. In fact, PUVA and UVB seem to induce selective apoptosis in the neoplastic T-cells.

The aim of the Italian e-Delphi consensus was to establish the first structured, expert-based consensus regarding the use of phototherapy for MF.<sup>5</sup> 28 dermatologists – with expertise in phototherapy and/or cutaneous lymphoma management from 21 Italian centers – participated in the e-Delphi panel. The consensus confirmed that phototherapy should be the first choice in the early stages of MF or in case of no response to topical steroids. NbUVB should be used as a monotherapy, while PUVA should be useful in case of folliculotropism or lack of response. On the other hand, the experts disagreed on the use of phototherapy for erythrodermic forms. Panelists confirmed that Fitzpatrick skin phototype assessment and/or minimal erythema dose (MED) are sufficient to estimate the starting induction dose for both nbUVB and PUVA. There is not adequate evidence in the literature to recommend the standard use of a maintenance phase phototherapy, but it could be evaluated case by case; when proposed, this should be short, avoiding the development of toxicity or disease progression. Less agreement was observed on the use of phototherapy in stages IIB-III A-III B, due to the high risk of progression to stage IV. Despite reports from the American consensus of a potential improvement with PUVA, retinoid PUVA, interferon2a-PUVA and Interferon2a-NB UVB, the Italian consensus encouraged the use of systemic therapies in an advanced stage of MF.<sup>6</sup>

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## Psoralen plus ultraviolet-A radiation therapy

PUVA is an UVL therapy treatment, using the sensitizing effects of a psoralen. Absolute contraindications to PUVA therapy are represented by xeroderma pigmentosum, lupus erythematosus with photosensitivity and pregnancy/lactation, while relative con-

traindications are the use of photosensitizing medications, history of skin cancer, previous treatment with ionizing radiation or arsenic, severe liver, renal, or cardiac disease, immunosuppression and age <10 years. The treatment regimen, given two to three times weekly, provides 8-12 J/cm<sup>2</sup> for each session, based on minimal phototoxic dose. The treatment can be gradually stopped by reducing the frequency of sessions. The side effects are represented by gastrointestinal disorders, skin xerosis and erythema, phototoxic and allergic reactions and autoimmune alterations. Moreover, PUVA has been associated with a dose-dependent risk of developing skin cancer, especially squamous cell carcinoma.<sup>7</sup>

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### Narrowband ultraviolet B light

NbUVB with a peak emission at 311 nm has also been shown to be effective for the treatment of early mycosis fungoides.<sup>8</sup> The treatment was given twice weekly, with the initial exposure dose being 70% of MED, with a subsequent increase of 20% at each treatment. The most commonly reported acute side effects, developing within 24 hours, are erythema, pruritus, burning, blistering, and xerosis. Generally, the erythema related to nbUVB develops at 2 to 6 hours after radiation and resolves largely in 48 hours. Also, herpes simplex virus reactivation has been observed.

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### Ultraviolet B light vs psoralen plus ultraviolet-A radiation therapy

Diederer *et al.*<sup>9</sup> demonstrated the efficacy of UVB therapy for early stages of MF; in fact, 81% of patients achieved complete remission and 19% achieved partial remission. The authors also reported that the same effective UVB dose is safer than PUVA regarding carcinogenicity, with the development of less side effects (*e.g.*, nausea). In addition, nbUVB (311 nm) is associated with lower cutaneous effects such as irritation and erythema, compared with broadband UVB. In patients with early-stage MF, they recommended starting with narrowband UVB therapy and, in case of progression or no response, switching to PUVA therapy.

A systematic review compared the efficacy and safety of PUVA vs. nb-UVB in patients affected by early-stage MF,<sup>10</sup> suggesting that PUVA may be an effective alternative to nb-UVB. Rattanakaemakorn *et al.*<sup>11</sup> confirmed the pivotal role of phototherapy, showing that 93.4% of patients affected by early-stage MF and receiving phototherapy as the first-line treatment, achieved complete remission. Moreover, they demonstrated that the presence of poikiloderma was associated with poor response, while age, gender and type of phototherapy weren't predictive factors. Zengarini *et al.*<sup>12</sup> analyzed the effectiveness of nb-UVB and PUVA on early MF, enrolling 75 patients. Patients treated with PUVA underwent therapy three times per week, with a starting UVA dose and each increase depended on the Fitzpatrick skin phototype. Patients were treated with nb-UVB two or three times weekly, with a starting dose and an increase per session depending on the skin phototype. The results demonstrated the similarity between the two options, without significant differences in clinical response; however, PUVA was associated with more adverse events.

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### Ultraviolet A light-1 therapy

Several studies confirmed the effectiveness of UVA1 in the treatment of early MF. Adışen *et al.*<sup>13</sup> showed a complete response in 63% of patients and partial response in 37% of patients after UVA1 treatment (30 J/cm<sup>2</sup> doses given 5 times weekly for 5

weeks). The therapy was well-tolerated, although a hyperpigmentation of the exposed skin was observed. "High-dose" UVA1 therapy was also investigated by Zane *et al.*,<sup>14</sup> in plaque-stage and tumor-stage MF. Thirteen patients affected by stage IB, IIB and III of MF, received 100 J/cm<sup>2</sup> UVA1 for 5 times weekly until clinical remission. The treatment, that was well-tolerated, showed a complete clinical and histological response on exposed skin. Also, Trovato *et al.*<sup>15</sup> investigated the role of UVA1, successfully used in patients with early MF and with good performance status. UVA1 phototherapy (45 J/cm<sup>2</sup> doses given 3 or 5 times weekly for 22 session) demonstrated a higher tolerability and a lesser possibility of developing secondary skin cancers compared to PUVA therapy. However, the devices may be expensive and can be used only in limited specialized centers.

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### Other treatments

Rupoli *et al.*<sup>16</sup> evaluated the long term efficacy of PUVA associated with interferon treatment. A total of 87 patients with early stage MF were enrolled into this retrospective study. They received subcutaneous IFN- $\alpha$ 2b and PUVA irradiation combination therapy for a median time of 14.6 months (range, 2-51.9). The overall response rate was 97.8% (n=85) and included complete remission in 80.5% of patients and partial remission in 11.5%. The best response was observed after a median of 5 months (range, 1-30). The FLASH study,<sup>17</sup> a phase 3, placebo-controlled, double-blind, multicenter randomized clinical trial, evaluated the efficacy and safety of synthetic hypericin ointment photodynamic therapy (PDT) in patients with early MF (stage IA- IIA). Hypericin, naturally found in plants (*Hypericum genus*), is a tumoricidal substance, which is activated by visible light. After 6 weeks of treatment, hypericin PDT was more effective than placebo. Significant improvements were observed in both patch and plaque type lesions, regardless of age, sex, race, stage, and prior therapies. Therefore, hypericin PDT is a clinical advance in the field of MF treatment, showing good response and a potentially long-term safety profile. Recently, a study demonstrated the successful role of 308-nm excimer laser in the treatment of early-stage MF,<sup>18</sup> obtaining complete response in 73.6% of the patients, with mild side effects. However, few data are available in the literature and further studies are requested in order to confirm the efficacy and the safety. Lastly, some studies demonstrated that MF can lead to reduction of quality of life (QoL) and a higher risk for depression and anxiety in affected patients.<sup>19,20</sup> Graier *et al.*<sup>21</sup> evaluated the role of PUVA on QoL, anxiety, and depression. Each patient completed the Dermatology life Quality Index (DLQI) and the Hospital Anxiety and Depression Scale (HADS) questionnaires before and after PUVA treatments. The results demonstrated that PUVA significantly improved overall QoL by reducing mean DLQI scores by 58.6% and HADS by 30%.

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### Controversial

According to the literature, UV radiations have an immune modulatory effect on the skin, inducing a Treg response,<sup>22</sup> but the role of UV upon skin-resident T-cells is not completely known. Jones *et al.*<sup>23</sup> evaluated the role of mutational signatures in CTCLs; in particular, they found a strong association between clonotypic UV signature 7 and CTCLs, specifically contributing 52% of the mutational burden in MF and 23% in Sezary syndrome. The identification of a clonotypic UV mutational signature in CTCLs confirms that environmental UV exposure has a role as a causal factor in the transformation of T-cells, both circulating and skin-resident.

## Conclusions

In conclusion, phototherapy plays a pivotal role in the treatment of MF, currently and largely used as first line in the early stages. Several studies of the literature confirmed the efficacy and safety of traditional regimens, such as nb-UVB and PUVA, although new options are recently emerging.

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