Phototherapy of Mycosis Fungoides

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INTRODUCTION
Phototherapy, specifically, ultraviolet B (UVB) phototherapy, and psoralen plus ultraviolet A (PUVA) photochemotherapy, has been a mainstay of treatment of mycosis fungoides (MF) for the last several decades. Initially, both types of phototherapy were used as monotherapy for early stage MF, but in recent years, the use has been expanded to include combinations of ultraviolet light (UVL) with systemic treatments in cases of treatment refractory early stage MF, and in patients with advanced MF. Although broadband (BB) UVB therapy was widely used in the past, currently most phototherapy delivered around the world is in the form of narrowband (NB) UVB. This article reviews the efficacy and safety profile of the most commonly used forms of phototherapy for MF.

ULTRAVIOLET B PHOTOTHERAPY IN MYCOSIS FUNGOIDES

Background
The clinically relevant electromagnetic radiation emitted by the sun consists of UVB, 290 to 320 nm and UVA, 320 to 400 nm.1,2 BB-UVB units available in clinical practice emit broadly between 270 to 390 nm with a peak at 313 nm. NB-UVB refers to a radiation source with a sharp emission peak between 311 and 312 nm.1

For a given dose, UVB at 300 nm is approximately 1000-fold more erythmogenic compared with UVA at 360 nm,2,3 but because of its shorter

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wavelength, UVB has less depth of penetration than UVA.

**Treatment Schedule**

Most centers recommend phototherapy 2 or 3 times a week; for practical convenience, twice-weekly phototherapy will clear the skin involvement, albeit at a slower pace than 3 times a week. It is best to have the treatments given at least 48 hours apart. Phototherapy directions are usually those recommended for psoriasis.\(^4,5\) The starting dose can be determined from minimal erythema dose (MED) or skin type; MED is usually utilized only in the face of a history of sun sensitivity. Increments in the light dose are best determined by a percentage of the previous dose based on the skin type and any unexpected or undesired erythema. Different phototherapy centers target a different endpoint and different maintenance schedule after clearing, which makes it difficult to determine overall efficacy and duration of response. Patients on NB-UVB may not be able to tolerate less frequent treatments than every 10 days due to burning. The United States Cutaneous Lymphoma Consortium (USCLC) has developed guidelines for MF that will hopefully alleviate this issue.\(^6\)

**Efficacy**

In a review of the published literature for both BB-UVB and NB-UVB, a complete response (CR) was defined as at least 90% clearance. The CR rates have been shown not unexpectedly to be greater for patch (>80%) than plaque disease (≤50%), but the majority of patients relapsed after discontinuing therapy.\(^7\)–\(^10\) BB-UVB has largely now been replaced by NB-UVB.

The published reported CR rates for NB-UVB have ranged from 54% to 90% in patients with Stage IA–IIA disease.\(^10\)–\(^26\) As with BB-UVB, patients with patch-only disease did better than those with plaques, but patients with one B (IB) disease did much better with NB-UVB versus BB-UVB in 1 study (78% vs 44% respectively).\(^10\) The relapse rate without maintenance therapy (defined as continued treatment post near clearing) varied from approximately 30 to 100%\(^11\)–\(^18\) versus 4% to 83% in those with maintenance.\(^16\)–\(^21\)

The literature describing the use of NB-UVB in combination with other treatment modalities in MF is sparse, and comparative studies of mono versus combination therapy are lacking. Case reports of NB-UVB combined with bexarotene suggest efficacy in MF.\(^27\)–\(^28\)

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**PSORALEN PLUS ULTRAVIOLET A THERAPY IN MYCOSIS FUNGOIDES**

**Background**

Psoralen, taken orally or applied topically, conjugates and forms covalent bonds directly with DNA following exposure to UVA, resulting in the formation of DNA-psoralen cross-links with inhibition of DNA replication.\(^29\)

**Treatment Schedule**

An optimized form of methoxalen, or 8-MOP, called Oxsoralen-Ultra, is the current oral formulation available in the United States. This should be dosed at 0.5 mg/kg 1 to 1.5 hours before exposure to UVA. There is also a 1% topical formulation available for localized treatment. PUVA treatments are given 2 to 3 times a week in the United States, potentially more frequently elsewhere in the world. As with NB-UVB, less frequent treatments take longer to achieve remission. The starting dose and incremental doses are based primarily on skin type as with psoriasis.\(^4,5\) Maintenance treatment is generally done as for NB-UVB, although it is possible for patients on PUVA to tolerate treatments even given as infrequently as once a month; there may be no need to reduce amount of UVL at a given treatment when decreasing the frequency.

**Efficacy**

Complete clearance rates in MF being 85% for stage IA, 65% for stage IB, and 85% for stage IIA disease.\(^19\)–\(^32\) Based on the experience of experts, patches and thin plaques are known to respond better to PUVA than thick plaques. Most physicians treating patients with MF do use some sort of tapering frequency when the patient has achieved a maximum response. Although expert opinion reflects that most MF experts do use some kind of maintenance PUVA because of the feeling that it prolongs remission, the literature is not as clear-cut. Querfeld and colleagues\(^33\) reported the long-term outcome of 66 patients with early stage MF (IA–IIA) who achieved a CR, most (94%) patients were then put on continuous maintenance therapy. Although 50% of the patients experienced relapse, the time to relapse was 39 months (range 2–127 months), and the other 50% of the patients had a sustained remission of a median duration of 84 months (7 years) (range 5–238 months, ie, 0.5–20 years). There was another study that compared the follow-up data between a group of patients with and without maintenance treatment after initial clearing phase of PUVA; there was no significant difference in the relapse rate or in the time to relapse between
the group of 25 early MF patients who stopped PUVA after clearing phase, and the group of 9 patients who received maintenance treatment for a further 15 treatments (range 0.3–10.5 months). The results of this study suggest that relatively short-term PUVA maintenance treatment may not necessarily slow disease recurrence.

PUVA is ineffective as a monotherapy for tumor-stage disease. Patients with erythroderma generally require a greater number of treatments to clear compared with patients with plaque-stage disease, but this may be because the dose of UVA utilized is much lower due to extreme photosensitivity. Blood involvement has been shown to be affected by PUVA therapy.

Combination therapy, primarily with retinoic acid receptor (RAR) retinoids, or bexarotene, a retinoid X receptor (RXR) retinoid, or alpha interferon, has been used in early disease to improve efficacy, possibly prolong remissions, or to treat those patients in whom lower response rates with PUVA alone are expected. Despite the fact that a combination of skin-directed and systemic treatment is usually considered more effective than either alone in MF, there are few studies to support this. A combination of PUVA with systemic therapy, however, may decrease the total UVA exposure and thus reduce long-term adverse effects. Although multimodality therapy including PUVA is frequently used in clinical practice, there are few published reports.

HAND/FOOT PSORALEN PLUS ULTRAVIOLET A

This is an important adjunct that can be used to treat the top and soles of feet that are otherwise excluded from UVA exposure while standing in the phototherapy box. This can be done at the end of the whole-body treatment with systemic psoralen on board or this can be done at an alternate time with prior application of topical psoralen.

SAFETY OF PHOTOTHERAPY

There are many common adverse effects shared by all forms of phototherapy, but there are some striking differences between NB-UVB compared with PUVA.

The most common acute adverse effects of all forms of phototherapy are erythema, maximum at 12 to 24 hours in NB-UVB with resolution at 48 hours and maximum at 48 to 96 hours in PUVA with resolution over the week following treatment. Other cutaneous adverse effects that are not uncommon to all forms of phototherapy include pruritus and stinging pain in circumscribed areas. These adverse effects can be managed by altering the dosage of light and holding therapy when clinically indicated. Photosensitivity to concurrent medications is usually caused by UVA and not UVB, but it can occur with either. Retinoids used in conjunction with phototherapy for MF have the greatest chance of increasing photosensitivity. Precipitation of polymorphous light eruption can occur with PUVA but is not usually seen with UVB. In some patients, phototherapy will unmask underlying MF lesions that are not apparent. Subungal hemorrhage, photoonycholysis, and melanonychia are common to PUVA but not UVB. Acute pigmented changes other than tanning are much more common with PUVA than UVB. PUVA induces immediate pigment darkening and persistent pigment darkening due to oxidation of preexisting melanin. Nausea may be seen with the intake of psoralen, and fatigue and headache have been reported with PUVA.

Many studies have been published regarding the adverse effects of long-term phototherapy. The most common are pigmented changes. With PUVA, patients may develop PUVA lentigos, which are usually persistent after treatment. Mottled guttate hypopigmentation can occur with either NB-UVB or PUVA.

Photoaging is another known adverse effect of long-term treatment with PUVA, but xerosis can be seen with either form of phototherapy.

Damage to the eye can occur with either form of phototherapy if protection is not given in the light box with UVL protective goggles. The risk with UVB is conjunctivitis or keratitis, and the risk with PUVA is cataracts. The risk of ocular damage with PUVA persists for 24 hours after taking psoralen until the medication is eliminated from the body. During that time, patients must wear UVA-protective wrap around sunglasses upon exposure to sunlight or if sitting by window glass that permits UVA to come through. A 25-year prospective study of patients treated with PUVA from a large US cohort study did not demonstrate an increased risk of either visual impairment or cataract formation with increasing exposure to PUVA, most likely because of the regular adherence to this recommendation for eye protection.

The main concern with both forms of phototherapy is an increased risk of skin cancer. Although there is no question that exposure to sunlight and sunburn can be associated with skin cancer, 2 publications summarizing more than 7000 patients with primarily psoriasis treated with either BB-UVB or NB-UVB did not show an increased risk other than those given both UVB and PUVA. In contrast, high cumulative exposure (>200 treatments or >2000 J/cm²) to oral PUVA
is associated with a dose-related increase in the risk of nonmelanoma skin cancer (NMSC), particularly squamous cell carcinoma (SCC).\textsuperscript{53–55} Although some US studies do not show an increased risk of melanoma in patients with psoriasis treated with PUVA,\textsuperscript{56} one 15-year follow-up US study has shown a higher risk of melanoma after a latency period of at least 15 years and/or high level of exposure (more than 250 PUVA treatments used as benchmark), with a relative risk of 3.1 if both were present.\textsuperscript{57} It should be noted that the duration of treatment in MF with PUVA is often greater than in psoriasis.

SUMMARY: PRACTICAL PEARLS FOR PHOTOTHERAPY

For patients with early stage MF

- Patches can be treated well with NB-UVB alone.
- Thick plaques or folliculotropic involvement are better served by PUVA than NB-UVB.
- Patients who have failed to clear on PUVA may benefit from NB-UVB.\textsuperscript{58}
- Systemic retinoids (acitretin or isotretinoin) specifically may be of value in patients with sun-damaged skin who are candidates for either NB-UVB or PUVA.\textsuperscript{59}
- Patients who have failed to clear with NB-UVB or PUVA alone, or who have associated poor prognostic factors, are best served with combination of phototherapy with a systemic agent.
- Because the goal of treatment is clearing, it is important to continue until reaching this end point and not to stop before it. Notably, it generally takes longer to induce a remission in MF versus psoriasis. Areas not accessible to UVL may be treated with topical steroids or targeted localized chemotherapy.
- Although extended periods of remission may be achieved with the use of maintenance treatment for either PUVA or NB-UVB, the decision to have it and the duration of this period is best determined by weighing the risk factors of chronic phototherapy treatment in a given patient including additional adverse effects, cost of therapy, patient time, psychological burden versus the risk of a clinical relapse with the potential need to restart therapy at frequency of 2 to 3 times per week.
- Most of the patients who respond to the first course of NB-UVB or PUVA therapy will respond to the second course.

For patients with advanced MF

- It is best to combine phototherapy with a systemic agent.
- Erythrodermic MF may be helped with either NB-UVB or PUVA alone, but because of the preexisting cutaneous erythema, it may be difficult in these patients to assess any burning from the UVL and hence to safely increase the UVL dose.
- PUVA may have an additional effect on the blood involvement in MF or se\'zary syndrome (SS) that NB-UVB does not.

REFERENCES