Therapeutic Guidelines - IADVL

Phototherapy for mycosis fungoides

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ABSTRACT

Background: Both phototherapy and photochemotherapy have been used in all stages of mycosis fungoides since they improve the symptoms and have a favourable adverse effect profile. **Materials and Methods:** We performed an extensive search of published literature using keywords like "phototherapy", "photochemotherapy", "NBUVB", "PUVA", "UVA1", "mycosis fungoides", and "Sezary syndrome", and included systematic reviews, meta-analysis, national guidelines, randomized controlled trials (RCTs), prospective open label studies, and retrospective case series. These were then arranged according to their levels of evidence. **Results:** Five hundred and forty three studies were evaluated, of which 107 fulfilled the criteria for inclusion in the guidelines. **Conclusions and Recommendations:** Photochemotherapy in the form of psoralens with ultraviolet A (PUVA) is a safe, effective, and well tolerated first line therapy for the management of early stage mycosis fungoides (MF), that is, stage IA, IB, and IIA (Level of evidence 1+, Grade of recommendation B). The evidence for phototherapy in the form of narrow-band UVB (NB-UVB) is less robust (Level of evidence 2++, Grade of recommendation B) but may be considered at least as effective as PUVA in the treatment of early-stage MF as an initial therapy. In patients with patches and thin plaques, NB-UVB should be preferentially used. PUVA may be reserved for patients with thick plaques and those who relapse after initial NB-UVB therapy. For inducing remission, three treatment sessions per week of PUVA phototherapy or three sessions per week of NB-UVB phototherapy may be advised till the patient achieves complete remission. In cases of relapse, patients may be started again on PUVA monotherapy or PUVA may be combined with adjuvants like methotrexate and interferon (Level of evidence 2+, Grade of recommendation B). Patients with early-stage MF show good response to combination treatments like PUVA with methotrexate, bexarotene or interferon-α-2b. However, whether these combinations hold a significant advantage over monotherapy is inconclusive. For late stage MF, the above-mentioned combination therapy may be used as first-line treatment (Level of evidence 3, Grade of recommendation C). Currently, there is no consensus regarding maintenance therapy with phototherapy once remission is achieved. Maintenance therapy should not be employed for PUVA routinely and may be reserved for patients who experience an early relapse after an initial course of phototherapy (Level of evidence 2+, Grade of recommendation B). Bath-water PUVA may be tried as an alternative to oral PUVA in case the latter cannot be administered as the former may show similar efficacy (Level of evidence 2-, Grade of recommendation C). In pediatric MF and in hypopigmented MF, both NB-UVB and PUVA may be tried (Level of evidence 3, Grade of recommendation D).

Key words: Guidelines, mycosis fungoides, phototherapy

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are a heterogenous group of non-Hodgkin lymphomas (NHL) of which mycosis fungoides (MF) is the most common form comprising about 65%. Mycosis fungoides has an indolent clinical course with a low risk of mortality in

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early disease [Table 1]. The histology is characterized by epidermotropism of small- to medium-sized atypical T lymphocytes with cerebriform nuclei, and presence of epidermal Pautrier's micro abscesses. Immunohistochemistry reveals the cell of origin to be the mature memory Tcells (CD^{3+}, CD^{4+}, $CD45RO^{+}$, CD^{8-}). Tcell receptor gene analysis shows a clonal re-arrangement in the majority of cases. Therapeutically, the natural course of the disease is not modified by any type of treatment. Progression to extracutaneous involvement is estimated to occur in up to 30% of patients and is associated with a poor prognosis.[1] Based on the current literature, it is recommended that early-stage mycosis fungoides should be initially treated with skin directed therapy (SDT).[2,3] These include topical therapies like corticosteroids, nitrogen mustard, and bexarotene; radiotherapy like total skin electron beam therapy, and superficial X-irradiation; and phototherapy.

The UV spectrum is arbitrarily divided into three sub-regions: UVA (320–400 nm), UVB (290–320 nm), and UVC (100–290 nm). The various forms in which phototherapy is administered include natural sunlight phototherapy (or heliotherapy), fluorescent tubes: UVA, PUVA (UVA + topical/systemic psoralens) and UVB. UVB phototherapy includes broadband (BB) UVB; of 290–320 nm and narrow band (NB) UVB of 311+/- 2 nm. The newer variants include targeted phototherapy like excimer laser and lamp (308+/- 2 mm). The various dermatologic indications of phototherapy are psoriasis, vilitigo, atopic dermatitis, patch/plaque stage mycosis fungoides, prevention of photodermatosis, pityriasis lichenoides chronica, scleroderma, uremic pruritus, acquired perforating dermatosis and mastocytosis.[4-6] Contraindications to the use of phototherapy include associated disorders with significant photosensitivity, lupus erythematosus and pregnant or lactating females (only for PUVA). The treatment may be used with caution in patients with history or family history of melanoma or non-melanoma skin cancer, exposure to ionizing radiation or arsenic, uremia and hepatic failure (for PUVA).

Table 1: TNMB staging of mycosis fungoides

Stage	T	N	M	Description
IA	T1	N0	M0	Localized patch/plaque <10% body surface area
IB	T2	N0	M0	Diffuse patch/plaque >10% body surface area
IIA	T1-2	N1	M0	Patch/plaque and lymphadenopathy
IIB	T3	N0-1	M0	Tumor, lymphadenopathy
III	T4	N0-1	M0	Erythroderma, lymphadenopathy
IVA	T1-4	N2-3	M0	Histologically involved lymph nodes
IVB	T1-4	N0-3	M1	Visceral involvement

BSA: Body surface area, LAD: Lymphadenopathy

Irrespective of the disease indicated, there are two regimens that are most commonly used; the first involves determination of the individual's minimum erythema dose (MED) or minimal phototoxic dose (MPD). Seventy percent of the MED value is used for the first treatment; thereafter therapy is given three times or more in a week with 20%, or 10% increments depending on local experience and skin type tolerance. Another approach, as commonly practiced in India, involves a standard starting dose (280 mJ/cm^2 for NB-UVB and 0.5 J/cm^2 for PUVA), with stepwise increase (usually 20%) depending upon the patient's erythema response.[7] The safe administration of photo (chemo) therapy requires the involvement of a dermatologist knowledgeable about the modality, trained staff to administer treatment, and an informed patient.

Goals of the guidelines

The present guidelines are aimed to systematically review the evidence regarding the use of phototherapy and photochemotherapy in mycosis fungoides, their effectiveness and adverse effects and on this basis, put forth guidelines for the practicing dermatologists regarding their use.

Methodology

An extensive literature search was performed to collect data on the use of phototherapy in mycosis fungoides. Relevant literature published till July 2014 was obtained from PubMed, EMBASE and the Cochrane Library. Keywords like "phototherapy", "photochemotherapy", "NBUVB", "PUVA", "UVA1", "mycosis fungoides", and "Sezary syndrome" were used for literature search. All systematic reviews, meta-analysis, national guidelines, randomized controlled trials (RCTs), prospective open label studies, and retrospective case series in the English literature mentioning these keywords were reviewed. However, individual case reports mentioning the efficacious use of various forms of phototherapy were not included.

Evaluation of the literature

Evidence assessment: To assess the methodological quality of each study included for efficacy analysis, a grade of evidence was assigned using the criteria in Tables 2 and 3.

Table 2: Levels of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies (e.g., case reports, case series)
4	Expert opinion, formal consensus

RCT: Randomized controlled trial

Table 3: Grades of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or
	A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
	Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or
	Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or
	Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or
	Extrapolated evidence from studies rated as 2+, or
	Formal consensus
D (GPP)	A GPP is a recommendation for best practice based on the experience of the guideline development group

NICE: National Institute for Health and Clinical Excellence, RCT: Randomized controlled trial, GPP: Good practice point

RESULTS

A total of 543 studies were evaluated, 107 of which fulfilled the criteria for inclusion in the guidelines. Other aspects of the interventions (e.g. safety and combination therapy) were evaluated in accordance with the publications available, but without conducting a complete, systematic review of the literature.

PUVA

Initial clearing regimen

There is a paucity of randomized controlled trials to prove the effectiveness of PUVA in mycosis fungoides. Hence, the recommendations are based on data derived from these few randomized controlled trials along with the prospective open labels studies and retrospective studies. PUVA has been tried in all stages of mycosis fungoides but is most successful in early-stage disease, i.e. less than stage IIa. Gilchrest *et al*. for the first time reported the successful treatment of nine patients with 8-methoxypsoralen plus UVA.[8] Briffa *et al.* in one of the largest prospective studies found PUVA to achieve remission in majority of the patients.[9] Subsequently, several studies have established the efficacy of PUVA although these are heterogeneous studies with differences in patient selection, treatment protocols, and outcome variables [Table 4].[10] Based on the data of five studies and a total of 244 patients, Herrmann *et al.* calculated the rate of complete remission after an initial course of PUVA to be 90% for stage IA, 76% for stage IB, 78% for stage IIA, 59% for stage IIB, and 61% for stage III disease (Level of evidence 2++) and similar figures have been reported by Hönigsmann *et al.* (with a mean duration of treatment being 2–5 months in stage IA-III MF).[11,12] Whittaker *et al.* in a recent well conducted RCT observed that of the 41 patients receiving PUVA monotherapy, complete and partial remission (PR) was observed in 71% patients in a median of 27.5 PUVA sessions.[13] The median duration of response was 9·7 months and the total UVA doses received were 107 J/cm^2 (Level of evidence 1+). Wackermangel *et al.* evaluated the efficacy of PUVA using 5-methoxypsoralen (5-MOP) versus 8-MOP and found the two to have comparable results in terms of PUVA therapy duration, number of treatments or cumulative UVA dose and relapse rates.[14]

Frequency of PUVA

PUVA in mycosis fungoides is generally undertaken according to the guidelines established for the treatment of psoriasis.[15] The rates of complete remission vary from 58% to 88% when 2–3 treatments per week are administered; 42–86% when the frequency is 3 times per week; and 64–89% when PUVA is administered 2–4 times per week (Level of evidence 2+).[10] Once a patient achieves complete remission, a confirmatory biopsy of a previously exposed site is often recommended, although the implication of complete remission without pathological clearance is unclear.

Table 4: Results of PUVA in cutaneous T-cell lymphoma (modified from Carter *et al.*)[10]

	Design	No. of patients	CTCL stage	Intervention	PUVA frequency and duration	Response to therapy	Maintainance regimen and relapse
Hodge *et al.*	Retrospective	6	I-IIB (stage 2 and 3)	PUVA	3/wk	Clinically 2 patients cleared completely Also assessed histological clearance	NR
Bleehen *et al.*	Retrospective	38	I-IVB (stage I-7; stage II-17, stage III-12)	PUVA	2-3/wk	Clinical improvement in 7 patients in stage I, 4 in stage II, 5 in stage III	1/wk to 1/mo
Gilchrest	Retrospective	11	7 plaque type; 4-erythroderma	PUVA	2-4/wk	7 CR and 3 achieved PR	Taper to 1/wk to 1/2 wk with remission in 4 patints for >2 years
Lowe *et al.*	Retrospective	10	9 with stage II/III MF and 1 with SS	PUVA	Every other day	Disease control in 9 patients with MF; improvement in SS	Taper to lowest suppressive dose
Niemi *et al.*	Retrospective	6	I-III	PUVA	NR	3 patients with patch stage and 1 with tumour stage-CR/PR, 2 with plaque stage-poor response	1/wk in 2 patients
Rotstein *et al.*	Retrospective	20	I-III	PUVA	2/wk	-	NR
Briffa *et al.*	Retrospective	73	I-IVB	PUVA	2-3/wk	-	Taper off
Molin *et al.*	Retrospective	51	Pretumor	PUVA	4/wk	CR 58%	2/wk or 4 every fourth wk or irregularly
Molin *et al.*	Retrospective	25	Tumor stage	PUVA with topical or systemic chemotherapy	4/wk	CR and PR in 14/17 patients with skin limited disease; 5/8 patients with extracutaneous disease	1/wk or 1wk/mo or irregularly
Warin *et al.*	Retrospective	56	I-IVB	PUVA	NR		NR
Hamminga *et al.*	Retrospective	11	II	PUVA	NR	-	1/3 wk
Honigsmann *et al.*	Follow-up study	44	IA-III	PUVA	4/wk	55% of stage IA and 39% of Stage IB remained disease free at 44 month follow up	Taper off
Powell *et al.*	Retrospective	19	I-IVB	PUVA	3/wk	7/10 patients of early disease showed CR	Taper off
Rosenbaum *et al.*	Prospective	43	IA-III plaque, tumor, erythrodermic MF and parapsoriasis	PUVA	2-3/wk	25 CR (mostly plaque and parapsoriasis patients Avg PUVA dose was 117 j/cm2	Taper to 1/mo 17 relapsed in avg 6.3 months
Rabbiosi *et al.*	Retrospective	39	IA-IIB	PUVA	4/wk	CR in stage IA patients, PR in stage IB/IIA	Taper off; Recurrences in 33% stage IA, 84% in stage IB and in all stage IIA and IIB patients

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Table 4: Contd...

	Design	No. of patients	CTCL stage	Intervention	PUVA frequency and duration	Response to therapy	Maintainance regimen and relapse
Abel *et al.*	Retrospective 10 year follow-up	29	Plaque type Erythrodermic	PUVA	2-3/wk	CR in 10- plaque type 7-erythroderma without sezary	1/wk decreased to 1/mo Most patients relapsed in 10-20 month
Nozickova *et al.*	Retrospective	6	I-IVB	PUVA	4/wk	Not available	Taper to 1/mo
Oguz *et al.*	Retrospective	65	I-IIIB; Ia-44 Ib-8; IIa-6; IIb-5; IIIb - 2	PUVA	4/wk	Stage Ia-PR/ CR-44/0; Ib-7/1; IIa-6/0; IIb-2/1; IIIb-2/0	Taper to 1/4-6 wk
Thomsen	Retrospective	69	I-II	PUVA and Re-PUVA	4/wk	73% CR	2/wk
Roenigk *et al.*	Retrospective	82 in PUVA 15 in PUVA+IFN	I-III and parapsoriasis	PUVA and PUVA+IFN	3/wk	51 CR in PUVA 12 CR in PUVA+IFN	Taper to lowest frequency 31 relapse
Herrmann *et al.*	Prospective	82	IA-IVA (83% in IA or IB)	PUVA	2-3/wk	CR in 53 patients	Taper to 1/mo Mean duration of CR in all stages 43 months 3 developed BCC and 3 SCC
Roupe *et al.*	Follow-up study	24	IA-IB	PUVA RT in resistant cases	2/wk	Patch and limited plaque stage: All went in CR	NR
Akaraphanth *et al.*	Retrospective	9	IA-IB Hypopigmented	psoralen UVA, UVB, and topical mechlorethamine	2-3/wk	CR-8 PR-1	1-3/wk
Tan *et al.*	Retrospective	5 childhood MF	IA-IB	PUVA in 5	3/wk		NR
Diederen *et al.*	Retrospective	35 21 with NBUVB	IA-IB	PUVA n NBUVB	2/wk	PUVA/NbUVB: CR- 71%/81 PR- 29%/19	NR
Soung *et al.*	Retrospective	51	IA-IIB (96% in IA or IB)	PUVA	3/wk	44 (86%) CR	Taper to 1/mo Mean duration of remission 27M
El-Mofty *et al.*	Retrospective	10	IA-IB	Rt-Lt comparision between 2 groups NBUVB-PUVA and PUVB-Nb-PUVA	3/wk	NBUVB and PUVA equally effective NBUVB as effective as NBUVB	None
Querfeld *et al.*	Retrospective	104	IA-IIA	Long follow-up after PUVA	2-3/wk	66/104 CR followed	Taper to 1/6 wk
Weber *et al.*	Retrospective	16	IA-IIA	Bath PUVA	4/wk	All patient cleared	For 2-4 week @ 2-3/wk
Anadolu *et al.*	Retrospective	113 101-early stage MF 12-late stage MF	I-IVB	PUVA, PUVA+INF-alpha	3/wk	CR with PUVA-80.4% in early disease CR with PUVA+INF was 57% in early disease	Taper off

Contd...

Table 4: Contd...

	Design	No. of patients	CTCL stage	Intervention	PUVA frequency and duration	Response to therapy	Maintainance regimen and relapse
Wackernagel *et al.*	Retrospective	38	IA-IIB	PUVA with 5-MOP (14) and 8 MOP (24)	2-4/wk	CR in 86% of 5-MOP and 92% of 8 MOP group	1-2/wk
Ahmad *et al.*	Retrospective	40 (28 with PUVA and 12 with NBUVB)	IA-IVA	PUVA and NBUVB	2-3/wk	With PUVACR=64% PR=21% No R=14%	None
Ponte *et al.*	Retrospective	95-PUVA 19-NBUVB	IA-IB, IIA		PUVA-4/wk NBUVB-3/wk	PUVA 62.1%CR 25.3% PR NBUVB 68.4%CR 26.3% PR	Taper off
Laws *et al.*	Retrospective	28-18 NBUVB 8 bath PUVA	I-IB	Bath PUVA and NBUVB in childhood MF	NR	CR in 82%	NR
Pavlotsky *et al.*	Retrospective	26	14 folliculotropic 12<IIA	Bath PUVA	0.2 mg/L 8-MOP bath f/b UVA Irradiation 3/wk	CR in 62% cases	NR

CTCL: Cutaneous T-cell lymphoma, ICR: Initial clearing regimen, MR: Maintenance regimen, NR: Not recorded, wk: Weeks, mo: Months

Bath PUVA has been utilized as a therapeutic modality in patients in whom oral psoralens cannot be given. Pavlotsky *et al.* studied the effectiveness of bath PUVA (0.2 mg/L 8-methoxypsoralen bath 3 times weekly followed by UVA irradiation at 0.3 J/cm^2 with fixed increments every second session) in the treatment of folliculotropic mycosis fungoides (14 patients) and NBUVB-refractory early-stage mycosis fungoides (12 patients).[16] A complete clinical response was achieved in 62% of patients after an average of 33 weeks and a cumulative radiation dose of 158 J/cm^2. In another study, bath-PUVA was shown to decrease CCR4(+) cells and Tregs in lesions of mycosis fungoides but did not induce circulating Tregs.[17] In a retrospective study by Weber *et al.*, complete remission was achieved in all 16 patients after a mean duration of 63 days requiring 29 treatments and a mean cumulative UVA dose of 33 J/cm^2. The time to relapse after complete clinical clearance was 45.6 (+/-9.2) weeks. The results were comparable to oral PUVA.[18] Bath PUVA has also been tried in childhood mycosis fungoides. In a retrospective review of 28 children, 79% of whom had hypopigmented mycosis fungoides, use of NB-UVB phototherapy and bath PUVA led to complete or partial remission in 19 out of 22 patients after a median of 4 months. In 7 out of 12 patients treated with NB-UVB, relapse occurred after a median of 4 months, whereas 4 out of 8 patients treated with bath PUVA relapsed after a median of 45.5 months.[19]

Relapse rates and disease-free interval

The relapse rates and disease-free interval after phototherapy are less well studied. Hönigsmann *et al.* followed up 44 patients treated with PUVA and found that 55.5% of patients with stage IA disease and 38.4% with stage IB disease remained in complete remission for more than 6 years, whereas all patients with T3 disease experienced relapses.[12] Roupe *et al.* reported follow-up of 24 patients with early-stage mycosis fungoides for 3–18 years treated with PUVA and noted long-term remission in nearly 50% of the patients.[20] Querfeld *et al.* followed up 66 patients who achieved complete remission with PUVA and reported 5- and 10-year disease-free survival rates for patients with T1 disease to be 56% and 30%, respectively, and for T2 disease to be 74% and 50%, respectively.[21] Survival rates at 5, 10, and 15 years did not differ between the non-relapse and relapse groups. The results with PUVA are comparable to those seen with topical chemotherapy and total skin electron beam radiation.[22,23]

Combination treatment with PUVA

PUVA has been combined with other systemic treatments (interferon-α [IFN-α] and retinoids)[24-26] to improve efficacy or in patients with insufficient response to PUVA alone. In a recent systematic review, it was concluded that no combination treatment has been demonstrated to be superior to monotherapy. However, in advanced stages of mycosis fungoides,

combining PUVA with IFN-α or retinoids did not improve response to treatment, a benefit that was seen with a combination of methotrexate with IFN-α.[27] In an open label trial by Stadler *et al.*, PUVA was combined with IFN-α in patients with stages I and II disease and the combination was found to be effective in inducing complete remission in 10 of 13 patients and partial remission in another 3 patients (Level of evidence 2+).[28] Nikolaou found the combination of IFN-α2b and PUVA to be an effective and safe treatment treatment-refractory early stage MF patients as well as treatment-naïve advanced stage patients (Level of evidence 3).[29] In patients with advanced disease, complete remission rates were 14% versus 37% in stage IIB and III/SS patients, respectively. Patients with early stage disease had a 2-year disease-free survival of 100% versus 27% for the advanced stage group ($P < 0.001$).

In a phase III randomized controlled trial by EORTC Cutaneous Lymphoma Task Force, Whittaker *et al.* observed that there was no significant difference in response rate or response duration in early mycosis fungoides in the PUVA/bexarotene group versus PUVA group.[13] However, there was a trend toward fewer PUVA sessions and lower UVA dose required to achieve complete clinical response in the combination arm. Cheeley *et al.* in a small retrospective chart review studied 32 patients with cutaneous T cell lymphoma (CTCL) of whom 29 had mycosis fungoides, 2 had Sézary syndrome, and 1 had CTCL not otherwise specified.[30] In all, 26 patients received acitretin in addition to another therapy such as NB-UVB or PUVA. The overall response rate was 59%. In a prospective phase II trial by Chiarion-Sileni *et al.*, of IFN-α-2a plus PUVA in patients with CTCL, 51 of 63 patients (Stage IA, $n = 6$; IB, $n = 37$; IIA, $n = 3$; IIB, $n = 3$; III, $n = 12$; IVA, $n = 2$) achieved complete remission (74.6%) or partial remission (6%) (Level of evidence 2+).[31] The median response duration was 32 months with a 5-year overall survival rate of 91% and the 5-year disease-free survival rate of 75%. In a multicentric prospective phase II clinical study by Rupoli *et al.* on 89 patients with early-stage IA to IIA mycosis fungoides treated for 14 months with low-dose IFN-α-2b (6–18 MU/week) and PUVA,[32] complete remission was achieved in 84% patients with an overall response rate of 98%; 6-month complete remission was associated with a non-confluent skin infiltrate on histology ($P = 0.044$) and 14-month complete remission with high epidermal CD1a + dendritic-cell density ($P = 0.030$). The combination protocol was successfully tolerated and the most common reason of failure was related to relapse and not to toxicity. Sustained remissions were achieved in 20% of patients. High CD8 + lymphoid T-cell density was associated with a lower relapse rate ($P = 0.002$).

NB-UVB

As with PUVA, uncontrolled trials and case series form the bulk of the evidence supporting its use in mycosis fungoides. NB-UVB is administered 2–3 times per week as the initial clearing regimen.[10] Most patients experience an erythema within 24 h, which decreases abruptly allowing follow up treatment at 48 h.[33] Milstein *et al.*, in 1982 for the first time reported the successful use of UVB in 31 patients with mycosis fungoides.[34] In a retrospective analytical study involving 143 patients with early mycosis fungoides treated with PUVA, NB-UVB, psoralen and NB-UVB, BB-UVB or BB-UVA, there was no statistically significant difference between the response to oral PUVA and NB-UVB.[35] The efficacy of NB-UVB has been addressed by a number of studies and case series [Table 5].[10,36-39] Gokdemir *et al.* concluded that in stage IA-IIA, complete remission can be achieved with a NB-UVB thrice weekly regimen in 54–91% of patients within 3–4 months (Level of evidence 2+).[40] In this study, all the patients with patch stage mycosis fungoides had a complete remission, whereas in patients with plaque stage disease, 60% patients had a complete remission and 40% had partial remission or no clinical response. The mean cumulative dose and the mean number of treatments was 90.15 J/cm^2 and 35.33, respectively, in patch stage mycosis fungoides compared with 90.67 J/cm^2 and 39.40, respectively, in plaque stage mycosis fungoides ($P > 0.05$). In a study by Hofer *et al.*, complete remission was achieved in five out of six patients after a mean of 20 treatments and 17.2 J/cm^2 cumulative doses, and. relapses were reported in all patients within a mean of 6 months after discontinuation of treatment.[41]

In a recent open label trial by Jang *et al.*, 11 (78.6%) of 14 patients achieved complete remission within a mean of 15.36 ± 5.71 weeks, 31.0 ± 7.4 treatments and a mean cumulative UVB dose of 31.31 ± 12.16 J/cm^2.[42] The remaining three patients achieved partial remission. Six of eleven patients relapsed after a mean of 8.5 ± 4.1 months. In one of the larger retrospective trials, Ponte *et al.* analyzed 95 patients treated with PUVA and 19 with narrow band UVB.[43] With PUVA,

Table 5: Results of NBUVB phototherapy in cutaneous T-cell lymphoma (modified from Carter *et al.*)[10]

Study	No. of patients	CTCL stage	ICR frequency	ICR duration	MR frequency	MR duration
Hofer *et al.*	6 (MF) 14 (smll plaque parapsoriasis)	IA-IB	3-4/wk	Until 95% clear CR in 19/20	None	None
Gathers *et al.*	24	IA-IB	3/wk	Until 95% clear CR in 54% 13/24	Taper off	4-6 mo
Diederen *et al.*	21	IA-IB	2/wk	Until clear CR in 17/21 PR in 4/21	NR	NR
Boztepe *et al.*	NbUVB14	IA-IIA	3/wk	Until 95% clear CR in 11/14 after mean of 25 sessions	Taper off	12-30 mo
El-Mofty *et al.*	20 patients - 10-half body NBUVB vs. PUVA 10- half body psoralen-NBUVB vs. PUVA	IA-IIA	3/wk	4 mo 48 sessions	None	None
Ghodsi *et al.*	16	IA-IB	3/wk	CR in 75%	CR in 65%	NR
Gokdemir *et al.*	23	IA-IIA	3/wk	Until 90% clear Patch group: CR in all Plaque group: CR in 3/5	CR in all pt of patch and 60% of plaque	2 mo
Pavlotsky *et al.*	68	IA-IB	3/wk	Until clear IA% 84 and IB 71% went in CR	Taper to sunlight	3.5 mo
Ahmad *et al.*	12	IA-IIB	3/wk	Until clear 50% CR 33% PR	None	None
Brazzelli *et al.*	20	IA-IB	3/wk	Until 95% clear CR in 90%	Taper off	2 mo
Kural *et al.*	23	IA-IB	3/wk	NR	Taper	NR
Clark *et al.*	8	IA-IB	3/wk	Until 90% clear	1/wk in 1 patient	NR
Xiao *et al.*	6	Early stage	2/wk	Until clear; 75% in CR	None	5 mo
Jang *et al.*	14	IA-IB	3/wk	Until >95% clear 11/14 CR 3/14 PR	None	None
Drucker *et al.*	17	11-IA-IB Rest ≥IIA		Until clear	NR	NR
Kanokrungsee *et al.*	11	Hypopigmented MF	2/wk	Until clear 7/11 CR	None	None
Koh *et al.*	9	IA-IIA	2-3/wk	Until clear	None	13.3

CTCL: Cutaneous T-cell lymphoma, ICR: Initial clearing regimen, MR: Maintenance regimen, NR: Not recorded, wk: Weeks, mo: months

59 patients (62.1%) had a complete remission, 24 (25.3%) had a partial remission, and 12 (12.6%) had a failed response. NB-UVB led to complete remission in 12 (68.4%) patients, partial remission in 5 (26.3%) patients, and a failed response in 1 (5.3%) patient. There were no differences in time to relapse between patients treated with PUVA and those treated with narrow-band UVB (11.5 vs. 14.0 months, respectively; $P = 0.816$). In another retrospective study of 56 patients comparing NB-UVB with PUVA, Diederen *et al.* found complete remission rates and mean relapse-free intervals to be similar between the two modalities and concluded that due to the practical advantages of NB-UVB, it might be a reasonable approach to a patient with early mycosis fungoides to start with NB-UVB and in case of lack of progression or lack of response switch to PUVA.[44] Similarly, Ahmad *et al.* in their retrospective analysis of 40 patients found both PUVA and NB-UVB to be effective in the treatment of early mycosis fungoides.[45] In another retrospective chart review, 15 of 17 patients with mycosis fungoides who were switched from PUVA to NB-UVB improved with better response in patients with earlier stage disease.[46]

In a small retrospective series of 11 patients with hypopigmented mycosis fungoides treated with NB-UVB twice weekly, 7 achieved complete remission

with a mean of 40 treatments and the other 4 patients had a partial remission. Relapse was seen in three patients after a mean of 10 months.[47] In another series of nine patients with hypopigmented mycosis fungoides, six patients received NB-UVB and three patients received PUVA.[48] In six patients who had complete remission, disease recurred in four (66.7%), and the disease-free interval ranged from 2 months to 6 years. In another study involving patients with hypopigmented mycosis fungoides from Egypt, phototherapy was effective in 86.7% of patients with success rate of 66.7% with NBUVB and 80% with PUVA.[49] Similar observations were earlier made by Akaraphanth *et al*.[50] In childhood mycosis fungoides, a retrospective analysis of nine children of East Asian descent with early-stage disease showed that treatment with NB-UVB led to complete remission in eight children with no significant adverse effects but all showed disease relapse after a mean of 13.8 months (range 4–36).[51]

UVA1

In a preliminary short case series, four patients with early-stage mycosis fungoides were treated with 1630–2710 J/cm^2 UVA1 given in 29–40 fractions. Complete remission was achieved in all cases.[52] In a study by Zane *et al.*, of the 13 patients (stage IB-III) who received high dose (100 J/cm^2) UVA1 phototherapy daily, 11 patients showed complete clinical and histological remission and another 2 had partial remission in contrast to the untreated control lesions.[53] In another study of 19 patients with mycosis fungoides treated with low-dose UVA-1 (20 or 30 J/cm^2), complete clinical and histological complete remission was achieved in 11 patients and partial remission in 3 patients after a mean cumulative dose of 1665 J/cm^2 and mean number of 73 exposure sessions.[54] In a study evaluating the efficacy of BB-UVA in the treatment of early-stage mycosis fungoides, 30 patients received either BB-UVA at 20 J/cm^2/session or PUVA three times/week for 40 sessions. Comparable clinical and histopathological improvement was noted in both groups.[55] The authors concluded that the use of BB-UVA in the treatment of early-stage mycosis fungoides is comparable or even superior to PUVA regarding efficacy and remission periods. Similar observations have been made by other authors.[56,57]

New developments in skin-targeted phototherapy include the excimer laser and the use of excimer light. There are seven studies, four of excimer laser and three of excimer light, all with good results.[58-65]

Need for maintenance therapy in mycosis fungoides

In a recent multinational survey among dermatologists, 88% of the respondents indicated that they used some form of PUVA maintenance after clearance had been achieved.[10] There was, however, no agreement on duration, frequency, and UVA-dose and a wide range of schedules were in use. At present, there is insufficient evidence for the benefit of PUVA maintenance [Table 6]. The recently published consensus of the EORTC suggested avoidance of maintenance therapy.[66] In their follow-up of nearly 28 months, Sanchez *et al.* observed that maintenance therapy with PUVA does not prevent relapse. A practical approach might be to reserve maintenance for patients who experience an early relapse after an initial course of PUVA and to adapt the schedule so as to minimize interference with the patients' quality of life (e.g. once weekly without further dose increments for 3–6 months).[67] Pavlotsky *et al.* used BB-UVB and NB-UVB for treatment of cutaneous T cell lymphoma and demonstrated no difference in relapse rate for those with and without maintenance therapy. Sixty one percent of patients with disease relapse could be re-cleared with a second initial clearing regimen of UVB.[36] Boztepe *et al.* treated patients with NB-UVB using maintenance therapy and thought the use of maintenance phototherapy was a logical next step and may prolong the duration of remission.[37]

In another retrospective study involving 31 patients followed up for a median of 55 months (20–120 months), relapse was observed in 11 (35.5%) patients, within a mean of 28.8 ± 18.2 months (median 33 months, range 4–59 months), whereas 20 (64.5%) patients stayed relapse-free for a mean of 54.2 ± 28.8 months (median 55.5 months, range 20–119 months). Patients received maintenance phototherapy with a median duration of 12 months (range 1–30 months) after achieving complete response.[68]

CONCLUSIONS

In treating mycosis fungoides, it may be inferred that in patients with patches and thin plaques, NB-UVB should be preferentially used and that PUVA should be reserved for patients with thick plaques and those who relapse after initial response to UVB. In late stage disease, PUVA may be combined with methotrexate, bexarotene or interferon as first-line therapy. However, in early stage mycosis fungoides, the evidence is insufficient whether any combination is superior to

Table 6: Maintainance therapy with NBUVB or PUVA in MF (from Carter *et al.*)[10]

Author	No. patients	CR	Maintenance				No maintenance			
			Continued remission		Relapsed		Continued remission		Relapsed	
			No.	Follow-up period mean±SD (range), mo	No.	TTR mean±SD (range), mo	No.	Follow-up period mean±SD (range), mo	No.	TTR mean±SD (range), mo
PUVA										
Abel *et al.*	29	17†	3	42±4.6 (37-46)	12	16.8	-	-	-	-
Ahmad *et al.*	28	18	-	-	-	-	-	-	18	Median 10 (2-36)
Akaraphanth *et al.*	8	7‡	-	-	4	25.5±14.2 (6-36)	1	24	-	-
Anadolu *et al.*	96	75	14	(60+)	61	NR	-	-	-	-
Briffa *et al.*	73	60	30	NR	25	NR	4	11.2	1	5
Gilchrest	11§	7	4	(24+)	-	-	-	-	6	NR
Honigsmann *et al.*	44	44	15	37±27 (6-84)	29	22±25	-	-	-	-
Powell *et al.*	19	8	5	16 (1-44)	3	NR	-	-	-	-
Querfeld *et al.*	104	66	31	NR	30	NR	2	55±43.8 (24-86)	3	64.3±61.1 (5-127)
Rosenbaum *et al.*	43	25	8	29.5 (2-58)	17	6.3 (1.5-14)	-	-	-	-
Soung *et al.*	51	44	16	NR	28	NR	-	-	-	-
Wackernagel *et al.*	38	34	2	NR	7	NR	4	NR	21	NR
Totals	544	405	128		216		11		49	
NB-UVB										
Ahmad *et al.*	12	6	-	-	-	-	-	-	6	Median 11.2 (5-23)
Boztepe *et al.*	14	11†	7	26.6±10.7 (17-43)	2	20.5±0.7 (20-21)	-	-	1	6
Brazzelli *et al.*	20	18	-	-	18	8 (3-17)	-	-	-	-
Clark *et al.*	8	6	-	-	1	1	3	20	2	<3, 40
Gathers *et al.*	24	13	9	8±2.8‡	4	3.1±2.0 (1.5-6)	-	-	-	-
Gokdemir *et al.*	23	21	20	11.3±7.1 (1-25)	1	7.0	-	-	-	-
Hofer *et al.*	6	5	-	-	-	-	-	-	5	5.85±5.88 (2.25-16.25)
Kural *et al.*	23	19	12	21.9±10.2 (3-36)	7	8.4±4.3 (3-16)	-	-	-	-
Total	130	99	48		33		3		14	

CR: Complete response, LOE: Level of evidence, NR: Not recorded, TTR: Time to relapse, SD: Standard deviation

monotherapy. Bath PUVA is another option especially when oral PUVA cannot be administered. However, more evidence needs to be generated on the efficacy of bath PUVA. Hence, it is reasonable to start with phototherapy alone and combine it with one of the alternative therapies in case of inadequate response or early relapse. Moreover, there are insufficient data to conclude which type of phototherapy and which schedule (e.g. in terms of dose increments, frequency, etc.) might be optimal. The same is true for maintenance treatments, for which efficacy has not yet been proven although they are widely used in clinical practice. Mycosis fungoides is rare in childhood. Hence, the usefulness of phototherapy is not clearly defined in children. Both NB-UVB and PUVA have shown efficacy in the treatment of childhood disease and variants such as hypopigmented mycosis fungoides. Since most of these studies are small case series, it is difficult to extrapolate the results to a larger population.

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