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Narrow band UVB (311 nm), psoralen UVB (311 nm) and PUVA therapy in the treatment of early-stage mycosis fungoides: a right–left comparative study

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Background: **Psoralen ultraviolet A (PUVA) is a widely used first-line therapy for treatment of early cutaneous T-cell lymphoma. Narrow band UVB (UVB-NB) (311 nm) has been recently introduced as another effective line of treatment. It is postulated that the efficacy of UVB-NB could be enhanced by addition of psoralen.**

Aim: **The aim of the present work was to compare the clinical and histopathologic efficacy of PUVA and UVB-NB in the treatment of early-stage MF (stages IA, IB and IIA), and to evaluate whether psoralen adds to the efficacy of UVB-NB or not.**

Patients and Methods: **Twenty patients (stage IA, IB or IIA) were divided into two equal groups: group I received UVB-NB on the right body half vs. PUVA on the left side of the body for 48 sessions, and group II received PUVB-NB on the right side of the body vs. PUVA on the left side for 36 sessions. The sessions were administered three times weekly.**

Results: **In group I, almost equal results were obtained on both sides, i.e., UVB-NB and PUVA were equally effective in the treatment of early stages of MF, both clinically and histopathologically. In group II, PUVB-NB was found to be as effective as conventional PUVA in the treatment of early-stage mycosis fungoides, also on both clinical and histopathological grounds.**

Conclusion: **UVB-NB phototherapy should be included among the initial therapeutic options of mycosis fungoides in view of its efficacy, convenience, and likelihood of fewer long-term adverse effects. Addition of psoralen does not seem to enhance its therapeutic efficacy.**

Key words: **comparative; mycosis fungoides; PUVA; PUVB-NB; stages I and IIA; UVB-NB.**

Mycosis fungoides is a chronic slowly evolving peripheral non-Hodgkin's T-cell lymphoma initially presenting in the skin and showing distinct clinical, histologic, phenotypic and genotypic features (1).

Psoralen ultraviolet A (PUVA) is a widely used first-line therapy for treatment of early cutaneous T-cell lymphoma (2). The overall effect on neoplastic T lymphocytes may be caused by preferential mitotic inhibition or killing of neoplastic T cells, in the skin or superficial capillaries (3); other PUVA effects in MF include psoralen adduct damage to cell organelles (e.g., mitochondria) and alterations in the immune system (4, 5).

The mechanism of action of UVB in cutaneous lymphomas is still unknown but it may decrease the antigen-presenting capacity of Langerhans cells and increase interleukin-2 and -6 production by keratinocytes. Increased tumor necrosis factor has also been detected after UVB irradiation. Possibly, UV light suppresses the function of the neoplastic population of clonal T cells in the skin and serves as an immune upregulator (6, 7). The earliest studies showed that narrow band UVB therapy was effective in clearing skin lesions of small plaque parapsoriasis and early stages of MF (8, 9). NB-UVB can produce complete clearance in 75% of patients with patch-stage MF involving less than 10% of the body surface area (10).

Aim of the study

The aim of the present study was to assess the difference between the therapeutic effectiveness of the well-established PUVA therapy vs. UVB-NB therapy, and to evaluate whether psoralen adds to the efficacy of UVB-NB or not. Two types of therapies were administered to the same patient to eliminate personal variations, when evaluating the response to therapy.

Patients and methods

Patients

Two separate study groups were engaged in two different studies, each of which recruited 10 patients with stage I or IIA MF. Group I studied the efficacy of UVB-NB vs. PUVA in early-stage MF after 48 sessions, while group II studied the effectiveness of PUVB-NB vs. PUVA after 36 sessions in the same condition. Finally, the results from both groups have been presented in this article.

Patients were subjected to full history taking, proper general examination and dermatologic examination together with routine investigations. A skin biopsy was taken from a corresponding region on each side of the body before therapy and then repeated every 18 sessions during the treatment protocol. The specimens were processed routinely and stained with H&E for light microscopic examination to study the histologic response.

Methods

Group I: Patients received UVB-NB on the right side only while the left side was covered by a half body suit. This was followed by psoralen ingestion. Then, 2 h later, the patients were exposed to UVA on the left side of the body while the right side was covered by a half body suit.

Group II: Psoralen was given orally 2 h prior to UV exposure, and then the right half of the body was treated with UVB-NB, while the other half was covered, followed by exposure of the left half to UVA while the right half was shielded.

8-Methoxy psoralen was provided to the patients in 10 mg capsules, and the dose was adjusted according to the patient's weight (0.7 mg/kg/body weight), given with meals. If patients complained of nausea, the dose of 8-methoxypsoralen was reduced to 0.5 mg/kg.

The starting dose at the UVB-NB side was 0.74 J/cm^2, according to ready calibrated tables supplied by the device. The dose was increased by 20% of the previous dose (as shown in the schedule) until obtaining mild erythema, thereafter that dose was maintained without further increase.

On the PUVA side the starting dose was 1 J/cm^2, which was increased every second session by 0.5 J/cm^2 until improvement occurred, and then the dose was fixed, with a maximum allowable dose at 7 J/cm^2/session.

All patients received three sessions per week.

Assessment:

(1) *Clinical assessment*:

The degree of improvement of the lesions globally as assessed by the physicians was graded as follows:

- Very good response ($\geq 80\%$) (complete response);
- Good response (80–60%) (partial response);
- Fair response (60–40%) (minor response); and
- Poor response ($\leq 40\%$) (no response).

(2) *Histopathological assessment*:

The degree of histopathological improvement of the lesions after treatment was graded as follows:

- Very good response: only sparse inflammatory infiltrate in the dermis;
- Good response: mild epidermotropism, sparse infiltrate and no atypical cells;
- Fair response: epidermotropism, dense band-like infiltrate $\pm$ atypical cells; and
- Poor response: epidermotropism, dense, deep dermal infiltrate, atypical cells.

Epidermotropism:

(a) No epidermotropism: −
(b) Few: +
(c) Numerous: ++
(d) With Pautrier's microabscesses: +++

Density of infiltrate:

1. Perivascular:
   (a) Sparse: +
   (b) Dense: ++
2. Band:
   (a) Interrupted: +++
   (b) Dense: ++++

Depth:

(a) Superficial: +
(b) Deep: ++

Atypical cells:

(a) Absent: −
(b) Present: +

Results

Group I (UVB-NB vs. PUVA)

The main clinical data of patients are presented in Table 1. Almost complete remission was achieved at the end of the treatment sessions (48 sessions, 4 months) in seven patients (70%) on both sides; three patients (30%) showed partial response on both sides, with no statistically significant difference (Table 2). Histopathologically, 20% of patients achieved almost complete clearance at the end of treatment protocol on both sides, with the remaining 80% showing partial histopathological remission equally on both

Table 1. Main clinical data of patients in group I

No.	Age (years)	Sex	Skin type	Duration	Extent (%)	Stage	Phase
1	11	Female	III	3 years	90	IB	Patch
2	11	Male	IV	2 years	80	IB	Patch
3	21	Male	IV	5 years	80	IB	Patch
4	32	Male	III	1 year	70	IB	Patch
5	45	Female	IV	2 months	60	IB	Patch
6	53	Male	IV	1 year	50	IB	Plaque
7	56	Male	IV	3 years	≤ 10	IA	Plaque
8	35	Female	III	1 year	60	IB	Patch
9	24	Male	III	3 years	20	IB	Patch
10	42	Female	III	1 year	80	IB	Patch

Table 2. Group I: comparison of the degree of clinical response of patients between the UVB-NB and PUVA sides

Clinical response ($n = 10$)	Session 18		Session 36		Session 48	
	UVB-NB	PUVA	UVB-NB	PUVA	UVB-NB	PUVA
Very good	2	3	2	1	7	7
Good	2	2	2	1	2	1
Fair	2	4	3	3	1	2
Poor	4	1	3	5	–	–
P-value	0.8		0.7		0.7	

UVB-NB, narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

sides. None of the patients at either side had disease progression (Tables 3 and 4). These results show that UVB-NB was as beneficial as PUVA in the treatment of early stages of MF (stages IA and IB).

As regards adverse effects, on the UVB-NB side, two patients suffered from severe erythema and one patient had a severe phototoxic reaction. As for the PUVA side, two patients had severe erythema and two patients had a severe phototoxic reaction.

Group II (PUVB-NB vs. PUVA)

The main clinical data of the patients are presented in Table 5. At the end of the treatment protocol (36 sessions, 3 months), eight patients (80%) achieved very good to good response on the PUVB-NB side, and seven patients (70%) achieved a very good to good response on the PUVA side clinically (Table 6). Comparably, 70% of patients achieved very good to good improvement histopathologically on the PUVB-NB side, and 60% of them achieved a very good to good response on the PUVA side (Tables 7 and 8). Only one patient showed disease progression on the PUVB-NB side, whereas no patient showed disease progression histopathologically on the PUVA side.

Table 3. Group I: comparison of the pathological response of the patients between the UVB-NB and PUVA sides at the start of treatment

No.	PUVA				UVB-NB			
	Epidermotropism	Density of infiltrate	Depth	Atypical cells	Epidermotropism	Density of infiltrate	Depth	Atypical cells
1	+++	+++	+	+	+++	+++	+	+
2	+	+	+	+	++	+	+	+
3	+	+++	++	+	++	+++	++	+
4	+	++	++	+	+	+++	++	+
5	++	+++	+	+	+	++	+	+
6	+	++	+	+	+	++	+	+
7	+	++++	+	–	++	++++	+	+
8	+	++	+	+	+	++	+	+
9	+	++	+	–	+	++	+	–
10	+	++	+	–	++	++	+	–

UVB-NB, narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

Table 4. Group I: comparison of the pathological response of the patients between the UVB-NB and PUVA sides after 48 sessions at the end of treatment

No.	PUVA				UVB-NB			
	Epidermotropism	Density of infiltrate	Depth	Atypical cells	Epidermotropism	Density of infiltrate	Depth	Atypical cells
1	–	+	+	–	–	+	+	–
2	–	+	+	–	–	+	+	–
3	+	++	+	–	–	++	+	–
4	+	++	++	–	+	+++	++	–
5	–	+	+	–	–	+	+	–
6	–	+	+	+	–	+	+	–
7	–	+++	+	–	–	+++	+	–
8	+	+	+	–	–	+	+	–
9	+	++	+	–	+	++	+	–
10	–	–	+	–	–	–	+	–

UVB-NB, narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

Table 5. Main clinical data of patients in group II

No.	Age (years)	Sex	Skin type	Duration	Extent (%)	Stage	Phase
1	24	Female	IV	5 years	8	IA	Patch
2	30	Female	IV	6 years	5	IA	Plaque
3	24	Female	IV	1 month	10	IA	Patch
4	13	Female	IV	3 years	70	IB	Patch
5	55	Female	III	2 years	80	IB	Patch
6	35	Female	IV	5 years	80	IB	Patch
7	50	Female	III	10 years	85	IIA	Plaque
8	50	Female	IV	20 years	20	IIA	Plaque
9	17	Male	IV	2 years	70	IB	Patch
10	21	Male	IV	4 years	85	IIA	Plaque

Table 6. Group II: comparison of the degree of clinical response of patients between the PUVB-NB and PUVA sides

	Session 18		Session 36	
Clinical response ($n = 10$)	PUVB-NB	PUVA	PUVB-NB	PUVA
Very good	–	–	5	2
Good	6	5	3	5
Fair	3	4	1	3
Poor	1	1	1	–
P-value	0.91		0.76	

PUVB-NB, psoralen narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

No side effects were reported in all patients except for one, who experienced severe erythema on the PUVB-NB side.

Discussion

PUVA is a widely used first-line therapy for treatment of early MF. It is effective in clearing early-stage MF and in prolonging remission with maintenance. Using PUVA therapy in the treatment of 82 patients with plaque-stage MF, complete clearance of lesions in 88% with limited plaque disease and in 51.9% with extensive plaque disease was observed. The mean duration of remission was 13 months for patients with limited plaque disease and 11 months for patients with extensive plaque disease. Therefore, it was concluded that in early-stage mycosis fungoides, PUVA could induce significant disease-free intervals (11).

UVB-NB was recently introduced among the treatment strategies of MF. Complete clearance of lesions in patients with small plaque parapsoriasis and early-stage MF within a mean time of 6 weeks could be achieved; however, in the follow-up period, relapses occurred within a mean time of 6 months (8). These

Table 7. Group II: comparison of the pathological response of the patients between the PUVB-NB and PUVA sides at the start of treatment

	PUVA				PUVB-NB			
No.	Epidermotropism	Density of infiltrate	Depth	Atypical cells	Epidermotropism	Density of infiltrate	Depth	Atypical cells
1	++	++	++	+	++	+++	++	+
2	+	+++	+	+	+++	+++	+	+
3	+++	++	++	+	++	+	++	+
4	++	++	+	–	++	++	+	–
5	++	+++	+	–	++	+++	+	+
6	+	++	+	–	++	+	+	–
7	++	+++	+	+	++	+++	+	+
8	++	+++	+	+	+	+	+	–
9	++	++	+	–	++	+	+	–
10	++	++	+	–	++	++	+	–

PUVB-NB, psoralen narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

Table 8. Group II: comparison of the pathological response of the patients between the PUVB-NB and PUVA sides after 36 sessions at the end of treatment

	PUVA				PUVB-NB			
No.	Epidermotropism	Density of infiltrate	Depth	Atypical cells	Epidermotropism	Density of infiltrate	Depth	Atypical cells
1	+	+	++	+	++	+	+	+
2	++	++	+	+	+++	++	+	+
3	+	+	++	+	–	+	+	+
4	++	+	+	–	–	+	+	–
5	–	–	+	–	–	–	–	–
6	+	+	+	–	–	–	–	–
7	–	+	+	–	+	–	–	–
8	+	+	+	–	–	–	–	–
9	–	+	+	–	–	–	–	–
10	++	+++	+	–	–	+	+	–

PUVB-NB, psoralen narrow band ultraviolet B; PUVA, psoralen ultraviolet A.

results were confirmed by the study of Clark et al. (9), who observed complete clearance of lesions in 75% of patients with early-stage MF. The mean duration of clinical improvement has been 20 months, and cases with partial response or poor histologic improvement were associated with rapid relapse.

Adding psoralen to UVB-NB (PUVB-NB) made it superior to UVB-NB alone in the treatment of psoriasis (12). In another study, it was found that PUVB was as effective as the conventional PUVA in the treatment of psoriasis (13).

The aim of the present study was to assess the difference between the therapeutic effectiveness of the well-established PUVA therapy vs. UVB-NB therapy, and to compare the effectiveness of PUVB and PUVA therapy in early-stage MF.

In group I, 70% of the patients achieved a very good response at the end of the treatment protocol on both sides. Statistically, there was no significant difference between the degree of response obtained after the use of UVB-NB and PUVA in the treatment of the early lesions of MF, stages IA and IB. UVB-NB and PUVA almost started to induce their therapeutic effect at the same onset and reached their maximal therapeutic effectiveness also at the same time. During the therapeutic interval, clinical observations on both sides were almost the same. Pathological assessment of the post-treatment biopsies revealed almost equal results on both the UVB-NB and PUVA sides at the end of the treatment sessions.

Our results are consistent with the results obtained by Diederen et al. (14), whose patients with early-stage MF achieved 81% complete remission and 19% partial remission on treatment with UVB-NB, whereas PUVA treatment led to complete remission in 71% and partial remission in 29% of patients. The mean relapse-free interval was almost equal for both treatment types; for their patients treated with UVB-NB, it was 24.5 months and for patients treated with PUVA, it was 22.8 months. In another study (10) 24 patients with stage I MF treated with UVB-NB, were followed up for a mean of 29 weeks. Upon discontinuation of treatment, four patients with complete response relapsed, with a mean time to relapse of 12 weeks, which is quite a short remission period in contrast to that mentioned by Diedren et al. (14).

In group II, 80% of patients achieved a very good to good response on the PUVB-NB side, and 70% obtained a very good to good response on the PUVA side at the end of the treatment protocol, with no statistically significant difference. One patient (case no. 1) showed very poor results on the right side (PUVB-NB) while clinical clearance was observed on the left side (PUVA). During the therapeutic interval, clinical observations on both sides were almost the same. Pathological assessment of the post-treatment biopsies revealed almost equal improvement on both the PUVB-NB and PUVA sides.

The effect of PUVA in MF may be a result of killing of neoplastic T cells, psoralen-adduct damage to cell organelles and alterations in the immune system (5, 6). Other effects are achieved by inducing apoptosis, especially by UVA, as it can trigger apoptotic cascade via p53-independent programmed cell death as well as protein-synthesis-independent preprogrammed cell death mechanisms. Zane et al. (15) detected reduced CD95 expression in MF cases treated with UVA therapy.

The mechanism of action of UVB-NB is by serving as an immune up-regulator and possibly by suppressing the function of the neoplastic T-cell population. UVB-NB phototherapy should be included among the initial therapeutic options of early-stage MF in view of its efficacy, convenience and likelihood of fewer long-term adverse effects. It has shorter irradiation times, which aids patient's compliance. It has no side effects of systemic psoralen (nausea, headache, etc.), and there is no need for protective glasses after treatment.

It seems likely that the mechanism of action of PUVB therapy is through both a direct therapeutic effect of 311 nm radiation on MF as well as through psoralen-mediated photochemical responses.

This is the first study in the published literature to evaluate the efficacy of PUVB-NB on early stages of MF. No detectable significant differences could be detected between both types of radiation, UVB-NB and PUVA, both clinically and pathologically, and psoralen did not seem to add much to the effect of UVB-NB in the treatment of stages I and IIA of MF. It was expected that UVA would induce a better response initially, because of its deeper penetration ability, but this was not the case in this study. However, perhaps the deeper effect of UVA will appear later in the form of delaying recurrences in the long term, and thus further studies for longer follow-up periods are needed for better judgment.

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