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CLINICAL REPORT

Narrowband UVB and PUVA in the Treatment of Mycosis Fungoides: A Retrospective Study

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Psoralen plus ultraviolet A (PUVA) is widely used as first-line therapy for treatment of mycosis fungoides. Narrowband ultraviolet B (NB-UVB) has also been shown to be effective for treatment of early mycosis fungoides. The aim of this retrospective study was to analyse the response to treatment and relapse-free interval for PUVA and NB-UVB therapies in mycosis fungoides. Forty patients were treated with PUVA or NB-UVB between 1980 and 2003. All patients had failed to respond to topical therapy or were unwilling to use it. PUVA therapy was used between 1980 and 1997. Thereafter, the choice between PUVA (twice a week) and NB-UVB therapy (three times a week) depended on stage and extent of the disease as well as on how far patients had to travel). Twelve patients (stage IA–IIB) were treated with NB-UVB and 28 patients (stage IA–IVA) with PUVA. No maintenance therapy was given. Six patients (50%) had a complete response, 4 (33%) had a partial response and 2 (16%) had a failed response to NB-UVB but had stable disease. PUVA led to a complete response in 18 (64%), a partial response in 6 (21%) and a failed response in 4 (14%) patients. The median relapse-free interval was 11.5 months in the NB-UVB treated group and 10 months in the PUVA group. The majority of the patients (79%) had stage IA and IB disease. Of these, 6 of 10 (60%) in the NB-UVB group and 13/21 (62%) in the PUVA group had a complete response to treatment. These results show that PUVA and NB-UVB are effective treatments for early mycosis fungoides. ***Key words: Mycosis fungoides; narrowband UVB; PUVA.***

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Mycosis fungoides (MF) is a form of cutaneous T-cell lymphoma characterized by progression from limited patches to more generalized plaques, tumours and lymph node or visceral involvement. The current treatment of early stage MF includes topical steroids, psoralen plus UVA (PUVA) photochemotherapy, narrowband UVB (NB-UVB), topical nitrogen mustard, topical bexarotene and electron beam irradiation. PUVA is widely used as first-line therapy for treatment of early MF. It has been shown to clear early MF and to prolong remission with maintenance therapy (1). NB-UVB has become popular recently, especially since reports of successful management of patients with early MF (2).

In this retrospective study, we report our experience of treating patients with MF with PUVA or NB-UVB between 1980 and 2003.

MATERIALS AND METHODS

The study was retrospective and did not require Hospital Ethics Committee approval. Patients with biopsy proven MF, treated with NB-UVB and PUVA between 1980 and 2003, were included in the study. They were identified from a departmental database. The time of the first diagnostic biopsy was taken as the time of diagnosis. The stage of the disease was determined based on the type and extent of skin involvement and presence of lymph node, visceral or blood involvement according to the Bunn & Lamberg system (3) and then transferred to the TNM (tumour, node, metastasis) system.

The following data were collected; age, sex, skin type, date of diagnosis, age at diagnosis, biopsy diagnosis, type of MF, stage of MF, sites and extent, extracutaneous involvement and investigations. NB-UVB and PUVA treatment data included: NB-UVB and PUVA treatment regimens, cumulative dose, number of treatments, response to treatment, relapse-free interval and adverse effects. PUVA therapy was established in our department in 1979 and NB-UVB was used to treat patients since 1998. The first course of treatment with NB-UVB and PUVA was used for comparison. Patients were treated until clear and maintenance therapy was not given. They were allowed to use emollients and mild-potency topical steroids in areas inaccessible to UV radiation. Patients were reviewed every 2 or 3 weeks during phototherapy and photochemotherapy, which is standard practice in our department.

Dosimetry

Prior to 1998, irradiance for PUVA therapy was according to the cabinet self-calibration system. This was checked with a calibrated Waldmann PUVA meter daily. After 1998, irradiance was measured each month by a person standing in the cabinet at 20 cm from the bulbs at 4 sides of the cabinet at 3 levels (shoulder, umbilicus, and lateral thigh), using a IL1400A radiometer and calibrated sensor for PUVA and NB-UVB. The mean of 12 readings was taken. Tables for UV time and dosage with 20% and 10% incremental scales were adjusted accordingly each month. The IL1400A radiometer and sensors were calibrated annually against a reference standard (A. Coleman, Medical Physics, Guys and St Thomas' Hospital Trust, London, UK).

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NB-UVB

Patients were treated with NB-UVB three times weekly in a Waldmann 5000 cabinet (Waldmann GmbH, Schwenningen, Germany) incorporating 24 100-W Philips TL-01 fluorescent lamps (311–313 nm). Eight 2×2 cm sites 1.5 cm apart on unaffected upper back skin were exposed to NB-UVB (50, 70, 100, 140, 200, 280, 390, 550, 770 and 1080 mJcm^{-2}) from a bank of 4 TL-01 fluorescent tubes. The first 8 test doses were used for patients with skin types I and II and the last 8 were used for those with skin type III. The minimal erythema dose was defined as the dose that caused just perceptible erythema 24 h after irradiation. The initial dose was 70% of the minimal erythema dose and thereafter 20% incremental increases were given at each visit. If the previous exposure caused grade I erythema, the next dose increment was reduced by 10% and if it caused grade II erythema, the penultimate exposure dose was given and incremental increases were omitted.

PUVA

Patients ingested 8-methoxypsoralen, (8-MOP crystalline tablets 10 mg of Deltapsoralen; Crawford Pharmaceuticals, Milton Keynes, UK) at a dose of 0.6 mg/kg, 2 h before UVA exposure. Patients were treated with PUVA three times weekly before 1998. Whole body UVA was given in a Waldmann 6000 cabinet, which contained 40 UVA fluorescent tubes, or a Waldmann 8001 cabinet containing 27 fluorescent tubes. They wore UVA protective spectacles for 24 h after treatment and males wore genital protection in the cabinet. The initial dose was given based on Fitzpatrick's skin type (skin type I=1.5 Jcm^{-2}, type II=2.5 Jcm^{-2}, type III=3.5 Jcm^{-2}). The incremental increase was given according to skin type each week (skin type I=0.5 Jcm^{-2}, type II=0.5 Jcm^{-2}, type III=1.0 Jcm^{-2}).

After 1998, treatment was based on minimum phototoxic dose (MPD) testing and 20% incremental increase was given after each visit, twice weekly. Eight 2×2 cm squares 1.5 cm apart on unaffected upper back skin were exposed to UVA, 2 h after ingestion of psoralen at a distance of 20 cm from a bank of 6 Waldmann UVA fluorescent tubes. The first 8 test doses (0.5, 0.7, 1.0, 1.4, 2.0, 2.8, 3.9 and 5.5 Jcm^{-2}) were used for patients with skin types I and II, and patients with skin type III received the second 6 doses (2.0, 2.8, 3.9, 5.5, 7.7, and 10.8 Jcm^{-2}). The MPD was defined as the dose that induced minimal perceptible erythema 72 h after irradiation.

Selection criteria for PUVA and NB-UVB

Patients were treated with PUVA or phototherapy if they failed to respond to topical therapy with emollients and/or potent topical steroids or were unwilling to use them and had symptomatic disease. PUVA therapy was selected between 1980 and 1998 before NB-UVB became available in our department. Thereafter, the choice between PUVA and NB-UVB was not necessarily related to stage or extent of disease. In some cases patients were treated with PUVA for convenience because it was administered twice weekly and suited patients travelling long distances who could not attend for NB-UVB three times weekly. The TNM stage of disease and treatment modality are shown in Table I.

Determination of clinical response

Patients were treated until clear and maintenance therapy was not given. Complete response (CR) was defined as the disappearance of all skin lesions, partial response (PR) as ≥50% improvement and failed response (FR) as <50% improvement.

Table I. *Response and relapse-free interval according to stage in narrowband UVB group and PUVA group*

Stage (*n*)	CR (*n*)	PR (*n*)	FR (*n*)	Median relapse-free interval (months)	Median cumulative dose (Jcm^{-2})
Narrowband UVB					
IA (6)	4	0	2	12.2	26.1
IB (4)	2	2	0	10.7	10.8
IIA (1)	0	1	0	6	22.7
IIB (1)	0	1	0	1	27.5
Total (12)	6	4	2	11.5	12.6
PUVA					
IA (7)	7	0	0	16.8	24.6
IB (14)	6	5	3	15.7	56.3
IIA (3)	3	0	0	14.3	120.2
IIB (2)	1	1	0	10	107.5
III (1)	1	0	0	4	20
IVA (1)	0	0	1	–	77
Total (28)	18	6	4	10	31.7

CR: complete response; PR: partial response; FR: failed response; PUVA: psoralen plus ultraviolet A; UVB: ultraviolet B.

Relapse was defined as clinically significant disease requiring further therapy. Relapse-free interval was defined as the period between CR and relapse.

Statistical analysis

The Mann-Whitney U test was performed (using Minitab software) on two samples to test the hypothesis that the two associated population medians were equal. These data are represented as median±interquartile ranges (IQR). Before performing this test, summary statistics were computed and side-by-side box-plots were produced to allow initial group comparison.

RESULTS

A total of 59 patients were diagnosed with MF, confirmed by histopathology, between 1980 and 2003. Forty patients, 26 men and 14 women with a mean age of 65.5 years (age range 28–82 years) were treated with PUVA and NB-UVB. Twenty-eight patients (70%) had skin type I, 3 (7%) had skin type II and 9 (23%) had skin type III. Potent topical steroids had been used by 18 of 28 patients in the PUVA group and 8 of 12 patients in the NB-UVB group. Two patients in the PUVA group had been treated with nitrogen mustard.

NB-UVB

A total of 12 patients, 7 men (58%) and 5 women (42%) with a mean age of 58.7 years (age range 28–77 years) were treated with NB-UVB therapy. The mean age at the time of diagnosis was 51.3 years (22–70 years). Seven patients had patch, 4 had plaque and 1 had tumour MF. The clinical stage at the time of treatment was; IA (*n*=6), IB (*n*=4), IIA (*n*=1) and IIB (*n*=1). The extent of MF was <10% in 6, and >10% in 6 patients.

NB-UVB treatment led to CR in 6 patients (50%), PR in 4 (33%), and FR in 2 patients (16%). Patients had a median of 19 treatments (8–53) with a median cumulative dose of 12.6 Jcm^{-2} (3.5–105.6). The median relapse-free interval for patients treated with NB-UVB was 11.5 months (1–23). Patients with patch-type MF had a median relapse-free interval of 12.2 months and with plaque-type MF, it was 10.8 months. The median relapse-free interval according to stage is shown in Table I.

PUVA

Twenty-eight patients, 19 (67%) men and 9 (33%) women, with a mean age of 69.6 years (age range 30–82 years) were treated with PUVA. The mean age at time of diagnosis was 59.6 years (age range 26–79 years). Sixteen (57%) patients had patch-type, 10 (35%) had plaque-type and 2 (7%) had tumour-type MF. The clinical stage at the time of treatment was IA (*n*=7), IB (*n*=14), IIA (*n*=3), IIB (*n*=2), III (*n*=1) and IVA (*n*=1). The extent of MF was < 10% in 7 patients and > 10% in 21 patients.

Eighteen (64%) patients had CR, 6 (21%) had PR and 4 (14%) had FR to PUVA. The median number of treatments received by patients was 19.5 (range 7–50) with median cumulative UVA dose of 31.7 Jcm^{-2} (range 10–215 Jcm^{-2}). The median relapse-free interval for patients treated with PUVA was 10 months (range 2–36 months). Patients with patch-type MF had median relapse-free interval of 12.1 months, 10.2 months for plaque-type and 8 months for tumour-type MF. The median relapse-free interval in patients according to stage is shown in Table II.

Mann-Whitney U test confirmed that there was no statistically significant difference between the number of exposures for each group shown in Fig. 1 (p=0.668). There was no statistically significant difference between the relapse-free intervals for NB-UVB and PUVA groups, as illustrated in Fig. 2 (p=1). A log transformation was applied to the two groups in each of the cases in this section and *t*-tests were used to compare the means of the transformed data (data not shown). The conclusions from this method of analysis were the same as those presented in this section. Although the data were not collected over the same time period, all of the data were used in the analysis.

The majority of the patients (79%) had stage IA and IB. Ten patients (83%) were treated with NB-UVB and 21 (75%) with PUVA. Complete response was recorded in 6 (60%) treated with NB-UVB and 13 (62%) treated with PUVA.

When the PUVA data was restricted to the 5 cases from 1997 to 2002 and the analysis in this section repeated, the conclusions reached were the same, but at the expense of ignoring more than half of the data (23 out of 40 cases).

Adverse effects

Treatment was well tolerated. Adverse effects included grade II erythema in 12 patients (NB-UVB=7, PUVA=5), nausea in 2 patients (PUVA) and pruritus in 2 (PUVA). No patient discontinued treatment because of adverse effects.

Follow-up

The median follow-up period for the NB-UVB group was 84 months (range 12–120 months), and 72 months for the PUVA group (range 12–310 months). All patients had disease recurrence. Six patients had further NB-UVB and 19 had PUVA therapy after disease rel-

Table II. Results of narrowband ultraviolet B (NB-UVB) and PUVA treatment in mycosis fungoides compared with data in the literature

Year (ref.)	Patients (*n*)	CR (%)	PR (%)	FR (%)	Relapse-free interval (months)	Maintenance treatment given	Exposures (*n*)
NB-UVB							
2000 (6)	8	75	25	0	20 (11–40)	both*	39.3
2005 (7)	14	78	7	14	20 (18–43)	yes	25
2006 (8)	23	83	17	0	16 (3–36)	yes	54.2
2002 (9)	24	54.2	29	16	3	both*	22.2
2003 (5)	21	81	19	0	25 (2–66)	ns	ns
1999 (2)	6	83	17	0	6 (2–15)	no	20
2005 (10)	16	75	18	7	4.5 (3–12)	no	27.0
This study	12	50	33	16	11.2 (5–23)	no	19.5
PUVA							
1985 (11)	43	58	9	32	29.5 (2–58)	yes	ns
1995 (1)	82	65	31	4	43 (1–55)	yes	ns
2005 (12)	104	63	ns	ns	39 (2–127)	yes	ns
2003 (13)	65	93	4	2	24 (13–39)	yes	ns
2003 (5)	35	71	29	ns	22.8 (1–43)	ns	ns
2006 (14)	38	89	ns	ns	15.5 (4–33)	both*	28.5
This study	28	64	21	14	10 (2–36)	no	19

*both, maintenance was given to a group of patients.

ns: not specified; CR: complete response; PR: partial response; FR: failed response; PUVA: psoralen plus ultraviolet A.

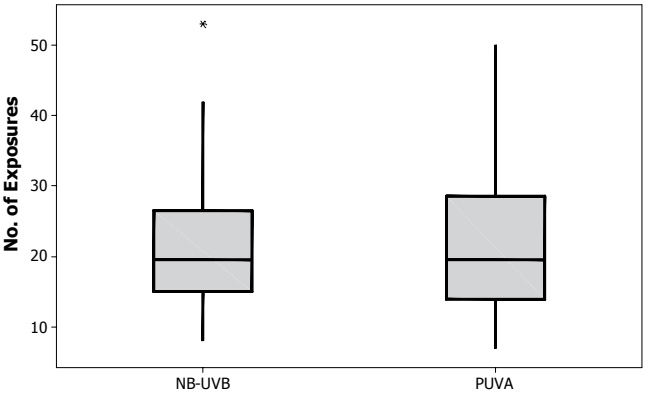

Fig. 1. Side-by-side box-plots for number of exposures in the narrowband UVB (NB-UVB) and psoralen plus ultraviolet A (PUVA) groups. The shaded boxes represent the first to third quartiles and horizontal lines are the medians. The asterisk represents an outlier at 53 exposures.

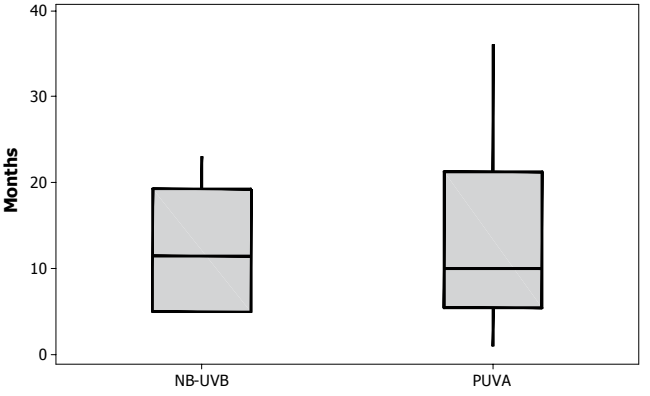

Fig. 2. Side-by-side box-plots for relapse-free interval in the narrowband UVB (NB-UVB) and psoralen plus ultraviolet A (PUVA) groups.

apse. Four patients had both NB-UVB and PUVA (data not shown). No patient received maintenance treatment with NB-UVB or PUVA.

DISCUSSION

The results of this study show that PUVA and NB-UVB are effective treatments for early MF. The majority of patients who responded to both treatments were stage IA and IB. Fifteen percent of patients failed to respond, including 2 with stage IA treated with NB-UVB and 3 with stage IB treated with PUVA. Patients with higher stage disease needed more exposures to achieve CR compared with stage IA and IB, regardless of which treatment they received. Similarly, the relapse-free interval was longer in patients with stage IA and IB compared with higher stages in both groups. The range of relapse-free interval was wider in PUVA group (2–36 months) compared with NB-UVB (5–23 months), but the medians and IQR were similar (Fig. 1). Maintenance treatment was not given, but on disease relapse, treatment was repeated.

To date, there are only 2 studies comparing the response of NB-UVB and PUVA in MF. El-Mofty et al. (4) treated 10 patients with stage IA and IB in a half-body comparison study. Patients received NB-UVB on the right side of the body and PUVA (8-MOP) on the left side, three times weekly for 4 months (48 sessions). There was no difference in response between NB-UVB and PUVA and CR was achieved in 70% of patients and 30% had a PR. No maintenance treatment was given in this study and relapse-free intervals were not specified. Diederen et al. (5), in a retrospective study, compared 21 patients treated with NB-UVB twice a week for a mean of 14 months (3–66 months) with 35 patients treated with PUVA (8-MOP) twice a week for a mean of 11 months (2–37 months). All patients had stage IA and IB disease. Seventeen (81%) patients had CR with NB-UVB and a mean time to relapse was 24.5 months. PUVA led to CR in 25 patients (71%) and a mean time to relapse was 22.8 months. These two studies showed favourable and equal responses of early stage MF to NB-UVB and PUVA. The relapse-free interval shown by Diederen et al. (5) was longer than in the present study. It is not clear if maintenance therapy was used in their study, but treatment was continued for a mean of 14 months.

Several open retrospective studies (5–14) and one prospective study (2) have shown the efficacy of NB-UVB and PUVA in MF, as shown in Table II. These studies reported CR in 54–83% of patients with NB-UVB and the relapse-free interval varied from 3 to 25 months. Similarly, 63–89% of patients cleared with PUVA and the relapse-free interval varied from 6 to 43 months. It is difficult to compare accurately the variation in the clearance rate and relapse-free interval because of differences in methodology and presentation of data in means or medians. The majority of patients in the studies were stage IA and IB. The number of exposures to clearance varies from 20 to 54. Maintenance treatment could be a factor in providing prolonged remission. The schedule of maintenance treatment after clearance was different in the studies, ranging from three times weekly for 3–6 months, twice weekly for 3–6 months, once bi-weekly for 3–6 months, to once a week for one year (2, 7). Although the patients who received longer maintenance treatment had prolonged relapse-free interval, as shown in most studies (see Table II), a recent study by Wackernagel et al. (14) suggested that maintenance treatment with PUVA (once or twice weekly for a mean of 15 treatments and a mean duration of 92 days) might not necessarily slow disease recurrence. They reported no significant difference in relapse-free interval between maintenance and non-maintenance groups. This was also supported by Rosenbaum et al. (11), who noted that MF recurred within about 6 months in all 25 of their complete responders, even though most of them (68%) had received maintenance therapy of once a month.

NB-UVB phototherapy has advantages compared with PUVA because patients do not have to take psoralen or wear UV protective glasses. Although UVB is a significant risk factor for non-melanoma skin cancer, comparable numbers of UVB treatments have less risk than PUVA therapy (15). PUVA is a potent mutagen and carcinogen. In experimental studies it induces a characteristic mutation in p53, with different type of DNA damage compared with UVB (16, 17). McGregor et al. (18) found p53 mutations in tumour-stage but not plaque-stage MF, which were similar to the mutation spectrum reported in non-melanoma skin cancers. Their data suggested a role for UV radiation in the pathogenesis of primary cutaneous lymphoma and a possible UVB-related step in the progression of MF from plaque-stage to tumour-stage MF disease. Therefore, maintenance treatment should be used with caution. In our unit we do not use maintenance therapy because MF is a chronic slow-progressing disease and patients will require repeated courses over many years. In the studies where maintenance treatment was used, it was given indefinitely from the start, following first induction. We consider that treatment should be stopped following initial clearance, in order to assess the duration of remission. Maintenance treatment could be considered for patients where remission time is short.

In our study, we found NB-UVB and PUVA to be effective and well tolerated in early MF. The CR and relapse-free interval were similar in both groups for those with early stage disease. It is not possible to comment on patients with disease more advanced than stage IA and IB because of insufficient numbers of patients. The results of this retrospective study and the literature would support the use of NB-UVB and PUVA for stage IA and IB MF. However, approximately 20% of our patients in these categories failed to respond to treatment. We favour NB-UVB for patch-stage MF and prefer PUVA for thicker plaque MF or for those patients who fail to clear or who have a short remission with NB-UVB, because of the more favourable long-term adverse effect profile associated with NB-UVB. However, this is a retrospective study with a small number of patients. Further larger prospective trials are needed to evaluate the first line of treatment in early MF.

Conflicts of interest: none to declare.

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