Original Article

Phototherapy for Early-Stage Mycosis Fungoides in Thais

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Objective: To study the efficacy of psoralen with ultraviolet A photochemotherapy (PUVA) and narrowband ultraviolet B phototherapy (NBUVB), for early-stage mycosis fungoides (MF) in Thais.

Materials and Methods: A retrospective medical chart review of 50 cases was performed. Demographic data, type of phototherapy, duration of treatments, clinical response, relapse, and adverse effects were analyzed. Comparative analysis of clinical response between hypopigmented MF and non-hypopigmented MF was performed.

Results: Fifty MF patients that were stage Ia to IIa were evaluated. Fifty-four percent of patients were treated with NBUVB, 20.0% with PUVA, 6.0% with ultraviolet A1, and 20.0% with combined phototherapy. Mean treatment duration was 7.0±2.3 months for PUVA and 7.6±4.4 months for NBUVB. Thirty patients (60.0%) had complete response and 17 (34.0%) had partial response. Clinical response between PUVA and NBUVB was not significantly different, however PUVA had less cases of relapse. Clinical response was better for hypopigmented MF patients than for non-hypopigmented MF patients.

Conclusion: PUVA and NBUVB are effective and safe for early-stage MF. Hypopigmented MF had better clinical response than non-hypopigmented MF.

Keywords: Asians, Mycosis fungoides, Phototherapy, Thai, Ultraviolet

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Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma, with clinical presentation normally occurring on the skin. Clinical presentation of MF is variable, with erythematous patches or plaques that can be localized or generalized in distribution. Less common features are hypopigmented patches and poikilodermatous MF. Typically, MF progresses slowly and painlessly[1-3]. Treatments vary according to stage of the disease. For early-stage MF (stages Ia-IIa), skin-directed therapies, such as topical agents (corticosteroids, nitrogen mustard, carmustine, and retinoids), narrowband ultraviolet B phototherapy (NBUVB), psoralen with ultraviolet A photochemotherapy (PUVA), photodynamic therapy, and radiation have shown effectiveness in resolving MF lesions[4,5]. Ultraviolet (UV)-based therapy is an established and commonly used treatment by dermatologists. Previous data supported the efficacy of PUVA in treatment of early-stage MF, with complete response (CR) reported in up to 71% of patients[6-9]. Recently, NBUVB (311 to 313 nm) has increased in popularity for treatment of MF but tends to be limited to the patch stage[10]. Very few studies focusing on phototherapy for treatment of early-stage MF in Asian people have been published. The objective of the present study was to evaluate the efficacy of phototherapy in treatment of early-stage MF in Thais. In addition, a comparative analysis of disease course and clinical response between hypopigmented MF and non-hypopigmented MF was performed.

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Materials and Methods

The present retrospective study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Fifty patients diagnosed as early-stage MF treated with phototherapy at the Department of Dermatology, Siriraj Hospital between January 1999 and December 2013 were included.

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Patients' clinical presentations were evaluated by dermatologists and diagnoses were confirmed by histological study. All patients with biopsy-proven MF were referred to a hematologist to exclude systemic involvement. Screening included the following studies, complete blood count, liver function test and lactate dehydrogenase, chest radiography, bone marrow biopsy, abdominal ultrasonography, and chest and abdominal computed tomography scan. Stages of MF were identified according to the TNM system[1]. Patients were advised and instructed regarding the course of disease, choice of phototherapy, efficacy of phototherapy, and side effects of phototherapy before receiving PUVA, NBUVB, or ultraviolet A1 (UVA1 340 to 400 nm). After physicians discussed with the patients, the treatment selected for each patient depended on the patients' decision. Patients with patches or thin plaques were more likely to treat with NBUVB. In contrast, thick plaques were more likely to treat with PUVA or UVA1. This was due to basic knowledge about penetration and effects of different wavelengths of phototherapy. However, there was no guideline or protocol for the selection. Frequency of treatment was two to three times per week for PUVA and NBUVB, and three to five times per week for UVA1 phototherapy.

The following patient data were collected and analyzed from medical records, demographic data (age, gender, diagnosis date, duration of disease, and family history), clinical presentation of MF (type of lesions, distribution, and symptoms), biopsy result, choice of phototherapy (PUVA, NBUVB, or UVA1), total number and duration of treatments, cumulative UV dose, clinical response, maintenance dose, relapse, and adverse effects. Clinical response was defined as CR for complete disappearance of clinical lesions, partial response (PR) for greater than 50% disappearance of lesions, and no response (NR) for less than 50% improvement in lesions. A comparative analysis of disease course and relapse between hypopigmented and non-hypopigmented MF was performed.

Data were analyzed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as frequency and percentage, or as mean ± standard deviation. The number of treatments, duration of treatments, clinical response between NBUVB and PUVA therapies, clinical responses, and relapse between hypopigmented and non-hypopigmented MF were compared using the Chi-square test with Yates' continuity correction or Fisher's exact test, as appropriate. A p-value of less than 0.05 was indicative of statistical significance.

Radiation source: Therapy was given in either a PUVA, NBUVB, or UVA1 cabinet. Conventional PUVA cabinet (Waldmann 8001K, Waldmann, Co., Villingen-Schwenningen, Germany) contained a bank of high-output UVA lamps. NBUVB cabinet (Daavlin Company, Bryan, OH, USA) contained a bank of TL-100W/01 fluorescent tubes (Philips Lighting, Roosendaal, The Netherlands) with peak emission at 311 to 312 nm. Therapy by PUVA and NBUVB was administered two to three times per week. For PUVA treatment, 8-methoxypsoralen (0.6 mg/kg) was given two hours before UVA irradiation. Patients who opted to receive UVA1 were irradiated three to five times per week at medium dose (50 to 60 J/cm^2) by a high-output source (Dermalight Ultra 1; Dr Hönle, Martinsreid, Germany) having an emission spectrum of 340 to 440 nm. The radiation protocols for PUVA and NBUVB were used as described before[11].

Results

Of the 50 patients, twenty-seven (54.0%) were female and 23 (46.0%) were male. Median age was 37 years (range 5 to 81). Most of the patients had Fitzpatrick's skin type IV (60.0%), followed by type V (28.0%), and type III (12.0%). Twelve (24.0%) patients were diagnosed younger than 15-year-old. Twenty-nine (58.0%) patients presented with hypopigmented patches, ten (20.0%) had erythematous plaques, ten (20.0%) had erythematous patches, and one (2.0%) had poikilodermatous MF. The most common locations were trunk and lower extremities (78.0%). Lesion appearing on the buttock, the head, the neck, and the intertriginous areas were less common. In most patients (52.0%), the lesions were asymptomatic. More than half of patients (60.0%) were treated with topical corticosteroids before definite diagnosis was made. For staging, 37 (74.0%) patients were stage Ia, 10 (20.0%) were Ib, and three (6.0%) were IIa (Table 1).

Twenty-seven (54.0%) patients were treated with NBUVB, ten (20.0%) with PUVA, three (6.0%) with UVA1, and ten (20.0%) with combined phototherapy. Four patients were switched from NBUVB to PUVA and six from PUVA to NBUVB due to ineffectiveness or intolerance to side effects of the prior type. Mean treatment duration was 7.0±2.3 months for PUVA and 7.6±4.4 months for NBUVB ($p>0.05$). The mean number of treatments was 45.8±19.2 and 49.0±22.6 for PUVA and NBUVB, respectively ($p>0.05$). Overall, 30 patients (60.0%) had CR, 17 (34.0%) had PR, and

Table 1. Demographic data, clinical characteristics, and staging of 50 patients with early stage mycosis fungoides

	n (%)
Age (years), Median (range)	37 (5 to 81)
Duration of disease (month), Median (range)	18 (2 to 156)
Sex	
Female	27 (54.0)
Male	23 (46.0)
Fitzpatrick's skin type	
Type III	6 (12.0)
Type IV	30 (60.0)
Type V	14 (28.0)
Type of lesions	
Hypopigmented patch	29 (58.0)
Erythematous plaque	10 (20.0)
Erythematous patch	10 (20.0)
Poikilodermatous	1 (2.0)
Location of lesions	
Trunk	39 (78.0)
Lower extremities	39 (78.0)
Upper extremities	36 (72.0)
Buttock	10 (20.0)
Head and neck	9 (18.0)
Intertriginous area	1 (2.0)
Symptoms	
Asymptomatic	26 (52.0)
Itching	23 (46.0)
Painful	1 (2.0)
Previous treatments before receiving phototherapy	
Topical corticosteroids	30 (60.0)
No treatment	15 (30.0)
Other	5 (10.0)
Staging (TNM classification)	
Ia	37 (74.0)
Ib	10 (20.0)
IIa	3 (6.0)

three (6.0%) had NR. The patients with CR receiving any type of phototherapy had mean treatment duration of 7.7±4.4 months and mean session of 52.0±27.3 times.

Clinical response between PUVA and NBUVB were not significantly different. Seven of 10 (70%) patients who received PUVA and 19 of 27 (70.4%) patients who received NBUVB had CR. Duration to clearance of MF lesions was 7.1±2.6 months for PUVA and 7.8±4.5 months for NBUVB ($p>0.05$). The number of treatments needed to bring about CR between methods was not different as 49.4±20.8 sessions for PUVA and 50.0±23.7 sessions for NBUVB. Patients who receive PUVA had less incidence of relapse compared to NBUVB, but the difference was not statistically significant ($p=0.07$) (Table 2).

Although this therapy is in the present time, there is still no definite protocol of maintenance phototherapy for the early stage MF. In the authors' practice, physicians usually offer the maintenance therapy for patients with CR. If the patients decided to receive further maintenance phototherapy, they would receive the same dose as last treatment of phototherapy with less frequency, which would be for NBUVB once a week or for PUVA once a month. Of 30 patients with CR, twenty-six (86.7%) received maintenance phototherapy. There was no significant difference in relapse rate between groups with or without maintenance after follow-up periods at the mean duration of 29.8±19.0 months.

Three patients were given UVA1 phototherapy. Two patients in stage Ia had CR. One patient in stage IIa with poikilodermatous-type MF did not respond to a two-month course of UVA1 radiation and was referred for electron beam radiation.

There were 29 hypopigmented MF patients in the present study. Eleven (37.9%) were male and 18 (62.1%) were female. Nine cases were previously reported[11]. Mean age of the 29 hypopigmented MF patients was 33.8±21.2 years. Distribution of hypopigmented patches was similar to distribution of erythematous patches and plaques lesions, as described above. Six (20.7%) patients were treated with PUVA, 18 (62.1%) were treated with NBUVB, and the remaining patients were treated with both PUVA and NBUVB. Among patients with hypopigmented MF, 72.4% had CR and 23.8% relapsed. With regard to efficacy, four of six patients who received PUVA and 14 of 18 patients who received NBUVB had CR, a difference for which there was no statistical significance ($p>0.05$). However, there was no relapsed case among hypopigmented MF patients treated with PUVA.

Five of 14 (35.7%) hypopigmented MF patients who received NBUVB and experienced CR, relapsed

Table 2. Number, duration and clinical response of PUVA and NBUVB monotherapy treatments (n=37)

	PUVA	NBUVB	p-value
Patients, n	10	27	
Number of treatments (sessions), Mean±SD	45.8±19.2	49.0±22.6	0.95
Duration of treatment (months), Mean±SD	7.0±2.3	7.6±4.4	0.82
Clinical response			
Complete response, n (%)	7 (70.0)	19 (70.4)	0.98
• Total number of treatment to clear the lesions (sessions), Mean±SD	49.4±20.8	50.0±23.7	0.95
• Duration of treatment to clear (months), Mean±SD	7.1±2.6	7.8±4.5	0.71
• Relapsed case, n (%)	0 (0.0)	6 (31.58)	0.07
• Disease free interval (months)		4.0±3.7	
Partial response, n (%)	3 (30.0)	8 (29.6)	

PUVA=psoralen plus ultraviolet A; NBUVB=narrowband ultraviolet B; SD=standard deviation

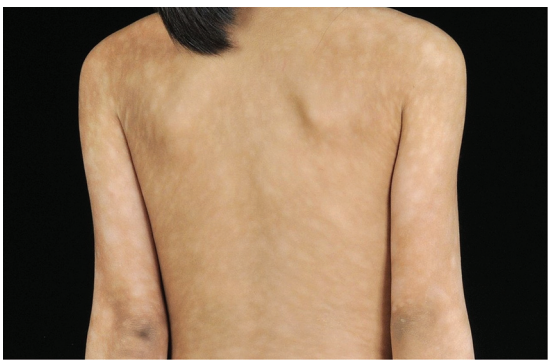

Figure 1. A patient diagnosed as early-stage hypopigmented mycosis fungoides.

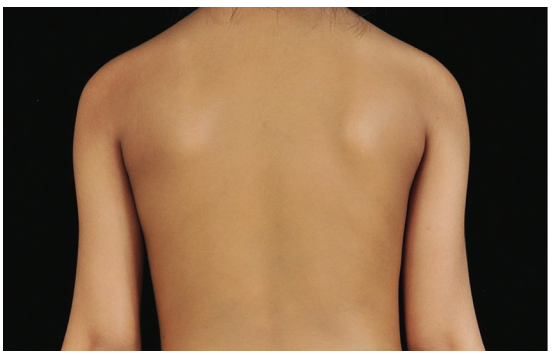

Figure 2. Clinical improvement after treated with narrowband ultraviolet B twice weekly for 8 months.

after disease free interval 6.6±5.6 months. Clinical response in hypopigmented MF was significantly better than in non-hypopigmented MF ($p<0.05$) (Figure 1, 2). All patients in the present study tolerated phototherapy well, no serious side effects were observed or reported (Table 3).

Discussion

There are a variety of treatment options available for early-stage MF, with phototherapy-based options being the most popular. Medications like topical corticosteroids, nitrogen mustard, and bexarotene are normally prescribed prior to phototherapy. In the present study, PUVA photochemotherapy and NBUVB phototherapy were studied for their effectiveness in treating early-stage MF. Fifty-eight percent of patients in the present study had CR from PUVA and/or NBUVB, which was consistent with CR rates from previously published studies (range 58% to 89% for PUVA and, range 50% to 83% for NBUVB)[12-14]. Hermann et al reported efficacy of PUVA in MF stage IA to III to be 59% to 90%, which is similar to the rate found in the present study (70%)[15]. Differences in cure rates can be affected by heterogeneity of patients, patient selection, treatment protocols, maintenance of phototherapy, sample size, and definition of clinical response. Hofer et al reported efficacy of NBUVB in six patients with patch-stage MF who received NBUVB three to four times per week for five to ten weeks to have CR up to 83.3%, while Gathers et al reported rates of 54.2% CR and 29.2% PR[13,16]. Trautinger suggested PUVA as the first choice for treating patients with later-stage MF or darker skin phenotype[7].

Comparing PUVA and NBUVB, the present study revealed similar CR rates (70% and 70.4%, respectively). Diederen et al reported efficacy of PUVA for 14 months and NBUVB for 11 months in

Table 3. Efficacy of phototherapy in hypopigmented and non-hypopigmented mycosis fungoides

	Hypopigmented MF n (%)	Non-hypopigmented MF n (%)	p-value
Number of patients	29 (58.0)	21 (42.0)	
Sex			
Male	11 (37.9)	12 (57.1)	
Female	18 (62.1)	9 (42.9)	
Age (years), Median (range)	34 (5 to 76)	43 (9 to 81)	
Clinical response			0.02*
Complete response	21 (72.4)	9 (42.9)	
Partial response	8 (27.6)	9 (42.9)	
No response	0 (0.0)	3 (14.2)	
Relapse	5 (17.2)	2 (22.2)	0.30

* p<0.05 indicates statistical significance

Table 4. Comparative studies of PUVA and NBUVB phototherapy in early-stage mycosis fungoides

	PUVA, n (%)				NBUVB, n (%)			
	Patients	CR	PR	NR	Patients	CR	PR	NR
Ponte, et al.[18]	95	59 (62.1)	24 (25.3)	0 (0.0)	19	13 (68.4)	5 (26.3)	0 (0.0)
Diederen, et al.[17]	35	25 (71.0)	10 (29.0)	0 (0.0)	21	17 (81.0)	4 (19.0)	0 (0.0)
Ahmad, et al.[14]	28	18 (64.0)	6 (21.0)	4 (14.0)	12	6 (50.0)	4 (33.0)	2 (17.0)
The present study	10	7 (70.0)	3 (30.0)	0 (0.0)	27	19 (70.0)	8 (30.0)	0 (0.0)

PUVA=psoralen plus ultraviolet A; NBUVB=narrowband ultraviolet B; CR=complete remission; PR=partial remission; NR=no remission

MF stages Ia and Ib of 71% and 81%, respectively. Ponte et al studied early-stage MF patients who received PUVA twice weekly for 15.6 months versus NBUVB three times per week for 12.3 months. They confirmed effectiveness but reported no significant difference in clinical response between the two regimens. From the present study, PUVA and NBUVB have similar effectiveness and can be used in initial treatment of early-stage MF. Duration and number of treatments have been reported in studies of Caucasian populations[17,18]. Those studies found that treatments ranged from 31 to 37 with duration of three to five months and found clearance of lesion to be associated with number and length of treatment. In Asian population, Jang et al reported the effectiveness and safety of NBUVB for early-stage MF in 14 Korean patients. Of those 14 patients, 78.6% had CR at a mean of 15.4 weeks and 31 treatments of NBUVB, which displayed shorter duration and lower number of treatments than the Thai patients shown in the present study[19]. Most of the present study cases had skin phototype IV to V, which is common in Southeast Asian populations. The need of the present study patients to have longer duration and more treatment sessions can be explained by the increased amount of melanin in the skin, which can inhibit UV penetration[20-22]. Comparative studies that also investigated NBUVB and PUVA in treatment of early-stage MF are summarized in Table 4. UVA1 phototherapy was used to treat three patients in the present study, with UVA1 treatment for MF also described in some previous reports[23-25]. Given the small number of patients that received UVA1 treatment in the present study, the authors were unable to comment or draw conclusions regarding the efficacy of this MF treatment option.

Hypopigmented MF is a variant of MF that is commonly seen in people of color. Hypopigmented MF has an earlier age of onset, as compared to classical MF. Interestingly, hypopigmented MF was the most frequent type of MF observed in the present study. In Singapore, a country with a variety of populations

(Chinese, Malay, and Indian), Tan et al reported 131 MF patients and found that classical-type MF (patches and plaques) to be most common (47.3%), with the hypopigmented MF variant found in 35.9%[26]. This is clinically compelling, because hypopigmented lesion can be diagnosed easily in darker skin phenotype patients. The present study found young women to be most affected by hypopigmented MF. The authors found that hypopigmented MF had better response to phototherapy, as compared to other types of MF. Kanokrungsee et al reported that 63.6% of hypopigmented MF achieved CR from twice weekly treatment by NBUVB, which is similar to the present study[27]. Two previous studies reported that PUVA can provide long-term remission more than NBUVB[11,28]. The present study demonstrated that hypopigmented MF responded well to either PUVA or NBUVB. However, relapse rate is high, similar to other types of MF.

NBUVB has an excellent safety profile. Erythema, pruritus, xerosis, and hyperpigmentation are predictable short-term effects of NBUVB. Long-term effects include photodamaged and photoaged skin. In PUVA, psoralen-related side effects include nausea, with chronic administration of PUVA being associated with lentigines and photocarcinogenesis. Based on the safety data, the authors recommend starting early stage of MF treatment with NBUVB and switching to PUVA if the disease is unresponsive to NBUVB or if disease progression is observed. Due to better skin penetration of UVA compared to UVB, PUVA has an advantage over NBUVB in thick plaque lesions and in darker skin.

The limitation of the present study is retrospective design with small number of patients in each phototherapy groups.

Conclusion

PUVA and NBUVB are both effective and safe for early-stage treatment of MF; however, disease relapse is common. Hypopigmented MF has better clinical response than non-hypopigmented MF.

What is already known on this topic?

PUVA photochemotherapy and NB-UVB phototherapy have been used to treat early-stage mycosis fungoides worldwide. However, only few studies have been done comparing the efficacy of both methods.

What this study adds?

Both PUVA and NBUVB are both effective and safe for the early-stage mycosis fungoides, however, PUVA has less relapse. Hypopigmented MF has better clinical response than non-hypopigmented MF.

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Conflicts of interest

The authors declare no conflict of interest.

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