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Treatment Response to Phototherapy in Patients with Mycosis Fungoides and Parapsoriasis

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Background: Early stage mycosis fungoides (MF) and parapsoriasis are treated by phototherapy techniques. In this study, we aimed to assess treatment responses to narrow-band ultraviolet B (NB-UVB) and psoralen plus ultraviolet A (PUVA) therapies in patients with MF and parapsoriasis in a comparative manner.

Materials and Methods: We retrospectively reviewed patients with early stage MF and parapsoriasis who underwent phototherapy in Phototherapy Unit of our clinic between 2008 and 2018. In all groups, data regarding phototherapy were recorded and evaluated statistically.

Results: In this study, 127 patients including 46 patients with early stage MF, 48 patients with small plaque psoriasis and 33 patients with large plaque psoriasis received phototherapy. PUVA therapy session rate was significantly higher in patients with MF while NB-UVB therapy rate was significantly higher in patients with SPP. Number and duration of sessions to achieve complete remission were significantly higher in patients with MF when compared to those with SPP while no significant correlation was found between MF and LPP. In addition, number and duration of sessions to achieve complete remission were significantly higher in patients with LPP than those with SPP. When patients groups were assessed according to phototherapy type given, it was seen that complete remission rate was significantly higher in MF patients received PUVA therapy than patients received NB-UVB therapy ($p<0.05$).

Conclusion: NB-UVB and PUVA doses to achieve complete remission in all patient groups were higher than those reported in the literature. In addition, PUVA therapy should be preferentially chosen in MF patients. In this study, we compared data regarding NB-UVB and PUVA in the treatment of early stage MF, small and large plaque parapsoriasis, providing a perspective to clinical practice.

Keywords: Phototherapy, mycosis fungoides, parapsoriasis, PUVA, NB-UVB

Introduction

Mycosis fungoides is an idiopathic, benign, cutaneous lymphoma. It is a frequently seen form of Cutaneous T Cell Lymphomas, a rare form of Non-Hodgkin lymphoma. The annual incidence is approximately 5.6:1,000,000 (1). The MF initially arises from skin. Malignant T Lymphocytes with cerebriform nuclei (MF cells) are localized at skin initially. In advanced stages, MF cells spread to lymph nodes and visceral organs. Skin lesions mainly develop at sun-protected areas and manifest with squamous, erythematous, atrophic patchy lesions. The

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disease progression is slow, advancing to plaque and tumor stage following a patchy stage. The diagnosis relies on a combination of clinical, histopathological and immunological data. TNMB (tumor-node-metastasis-blood) system is used for staging. The patients with early-stage MF [stage IA (T_1, N_0, M_0, $B_{0/1}$), stage IB (T_2, N_0, M_0, $B_{0/1}$), stage IIA ($T_{1/2}$, $N_{1/2}$, M_0, $B_{0/1}$)] can be treated effectively by skin targeting therapies such as PUVA/NB-UVB, localized radiotherapy or topical corticosteroid/nitrogen mustard/bexarotene (2).

Parapsoriasis is a rare, idiopathic, chronic a skin disease characterized by erythematous, squamous patchy lesions with mild atrophy, which are generally seen in sun-protected areas of trunk and extremities. The parapsoriasis is clinically classified into two groups according to the extent of lesions. Small plaque parapsoriasis (SPP) refers to lesions <5 cm with the digitate appearance which tended to localized at lateral aspects of the trunk. Large plaque parapsoriasis (LPP) refers to lesions >5 cm characterized with patch lesions which may be poikilodermic (telangiectasia, atrophy and mottled pigmentation,) in some occasions. It is thought that both forms represent a cutaneous T Cell lymphoproliferative disorder. Both forms may persist over the years. Although SPP is considered as a benign disorder without malignant potential, there are MF cases, which were diagnosed as SPP previously. Progression to MF is seen in approximately 10-30% of cases with LPP. Potent topical steroids are first-line therapy if parapsoriasis lesions are local. Phototherapy with broadband UVB, NB-UVB or PUVA is recommended if lesions are diffuse or refractory to topical steroid therapy (3).

In phototherapy, the induction phase is defined as the time from onset of therapy to complete recovery of lesions. The complete remission is defined as the disappearance of lesions. The remission is defined as the clinically lesion-free period while relapse is defined as a marked disease state requiring treatment (4).

Materials and Methods

In this study, we retrospectively reviewed 46 patients with early MF and 81 patients with parapsoriasis who underwent phototherapy in Phototherapy Unit of Hatay Mustafa Kemal University, Medical Faculty between 2008 and 2018. The patients were assessed regarding age, gender, duration of complaints, type of phototherapy, complete remission, number and duration of sessions to achieve complete remission, partial remission, cumulative UV doses, number of sessions, duration of maintenance therapy, relapse, time from complete remission to relapse, number of phototherapy repetitions, conversion to another form of phototherapy, comorbid diseases and treatment delay,combination therapy.

The patients with incomplete data and those who received phototherapy in another center were excluded from the study. SPSS v21 performed statistical analyses. The distribution of continuous variables was assessed by using the Kolmogorov-Smirnov test. Correlations between the groups regarding continuous variables were assessed by Kruskal-Wallis and Mann Whitney-U tests. Categorical variables were assessed by Fisher's exact test/Chi-square test. P value<0.05 was considered as statistically significant.

Results

In this study, we assessed data from 127 patients including 46 women (36.2%) and 81 men (63.8%). Of the patients with early-stage MF (n:46; median age: 50 years; range: 13-73

years), 78.3% received PUVA therapy while 21.7% received NB-UVB therapy. Of the patients with parapsoriasis (n:81), 48 patients had SPP (n:48; median age: 41.5 years) while 33 patients had LPP (n:33; median age: 54 years). Of those with SPP, 68.75% received NB-UVB while 31.25% received PUVA therapy. Of those with LPP, 45.5% received NB-UVB while 51.5% received PUVA therapy and 3% received local PUVA therapy. The type of phototherapy was selected based on contraindications and compliance in an individualized manner. Systemic NB-UVB and PUVA phototherapy were given in a Waldmann UV 7002 cabinet equipped with Philips 120W TL-01 NB-UVB and UVA lamps. Local PUVA phototherapy was given via Waldmann UV 181 AL equipped with Philips PL-L 36W UVA lamps. The NB-UVB, PUVA or local PUVA phototherapy was given in 3 non-consecutive days per week. In all patients, the initial dose of phototherapy was determined according to Fitzpatrick skin type.

Table-1 shows data regarding phototherapy in patients with SPP, LPP and MF, and p values. When patients with MF, SPP, and LPP were compared, no significant differences were found in age, gender, duration of complaints, cumulative UV doses, number of sessions, duration of maintenance therapy, partial remission rate (50% clearance), relapse, time from complete remission to relapse, number of phototherapy repetitions, overall follow-up, treatment discontinuation, conversion to another form of phototherapy in patients with partial remission, comorbid diseases and combination therapies. The number of sessions and duration to achieve complete remission was significantly higher in MF when compared to those with SPP, but no significant difference was found between MF and LPP.

Number of sessions and duration to achieve complete remission was significantly higher in patients with LPP than those with SPP. Besides, NB-UVB was more commonly selected in patients with SPP while PUVA therapy was more frequently selected in MF patients. Also, when groups were assessed according to phototherapy type given, it was found that complete remission rate was significantly higher in MF patients received PUVA therapy when compared to MF patients received NB-UVB therapy ($p<0.05$). Mean cumulative dose was 69.9 J/cm^2 in SPP, 86.4 J/cm^2 in LPP and 83.5 J/cm^2 in MF among patients received NB-UVB therapy whereas 277.6 J/cm^2 in SPP,313.8 J/cm^2 in LPP and 421.0 J/cm^2 in MF among patients received PUVA therapy.

The mean number of sessions to achieve complete remission was 56 in SPP, 76 in LPP and 78.5 in MF among patients received NB-UVB therapy, whereas 56.5 in SPP, 68 in LPP and 68 in MF among patients received PUVA therapy. Mean time to achieve complete remission was 5 months in SPP, 7 months in LPP and 6.5 months in MF among patients received NV-UVB therapy, whereas 5 months in SPP, 6 months in LPP and 8.5 months in MF among patients received PUVA therapy.

Discussion

It is known that phototherapy is beneficial in treatment of early-stage MF and parapsoriasis. NB-UVB therapy is a phototherapy method that uses light at 311-312 nm. The NB-UVB exerts its effects on the epidermis and superficial dermis layers of skin. PUVA is a phototherapy technique that involves the use of artificial light at 320-400 nm following oral methoxypsoralen. The PUVA penetrates more profoundly than NB-UVB, including mid-dermis layer of skin.

Table 1. Data regarding phototherapy in patients with SPP, LPP and MF and p values

Variables	SPP (n: 48)	LPP (n: 33)	MF (n: 46)	p
Gender (female/male)	15/33	11/22	20/26	0.431
Age	41.5 (18-81)	54 (7-81)	50 (13-73)	0.116
Duration of complaints (month)	24 (1-156)	24 (1-120)	33 (1.5-180)	0.3
Phototherapy type: number of patient (%) NB-UVB PUVA Lokal PUVA	33 (68.75%) 15 (31.25%) -	15 (45.5%) 17 (51.5%) 1 (3.0%)	10 (21.7%) 36 (78.3%) -	0.001
Treatment discontinuation number of patient (%)	9 (18.75%)	3 (9.1%)	11 (23.9%)	0.238
Complete remission number of patient (%)	39 (81.25%)	29 (87.9%)	33 (71.7%)	0.29
NB-UVB PUVA	25 (75.8%) 14 (93.3%) *P=0,148*	14 (93.3%) 15 (83.3%) *P=0,15*	4 (40%) 29 (80.6%) *P=0.006*	
Duration of sessions to achieve complete remission (month) NB-UVB PUVA Local PUVA	5 (2-17) 5 (3-8) -	7 (3-14) 6 (3-15) 1 (12)	6.5 (3-15) 8.5 (2-10) -	0.007
Number of sessions to achieve complete remission NB-UVB PUVA Local PUVA	56 (23-132) 56.5 (37-74) -	76 (32-115) 68 (24-155) 1 (48)	78.5 (24-107) 68 (39-195) -	0.005
Duration of maintenance therapy (month) NB-UVB PUVA	1 (0-5) 1.5 (0-14)	1.5 (0-5) 1.5 (0-7)	0 (0-2) 2 (0-22)	0,91
Number of sessions of maintenance therapy NB-UVB PUVA	4 (0-17) 6 (0-32)	4 (0-17) 5 (0-13)	4 (0-7) 5 (0-22)	0.39
Cumulative dose (J/cm^2)	69.9 (10.4-224.2)	86.4 (16.6-209.8)	83.5 (14.3-144.6)	0.68
NB-UVB PUVA Local PUVA	277.6 (80.7-895)	313.8 (126.1-1100.2)	421 (84.5-1648)	0.131
	-	578.5	-	
Partial remission and conversion of phototherapy number of patient (%)	0	1 (%6.7)	2 (%4,4)	0.27
Relapse number of patient (%)	5 (12.5%)	5 (16.7%)	6 (17.1%)	0.82
NB-UVB PUVA	1 (4%) 4 (26.7%) P=0.56	1 (6.7%) 4 (26.7%) P=0.33	2 (33.3%) 4 (13.8%) P=0.268	

Abbreviations. SPP (small plaque parapsoriasis), LPP (large plaque parapsoriasis), MF (mycosis fungoides), NB-UVB (narrowband ultraviolet B), PUVA (psoralen plus UVA). Data are given as median (min-max) or percentages.

There is no standard approach regarding optimum duration of NB-UVB or PUVA in the treatment of MF. The treatment is given generally in 3 non-consecutive days per week. The duration of therapy varies in each patient and treatment is maintained until complete remission. In MF, there is no consensus regarding need or duration of maintenance therapy. Given that total dose will be increased remarkably bymaintenance therapy, short-term maintenance therapy will be better in order to avoid cumulative toxicity and to take care of benefit-risk ratio. An individualized treatment plan should be established treatment response and comorbid disorders in each patient (4-6). In cases refractory to treatment or those with unsatisfactory response to treatment, systemic PUVA plus interferon (IFN-α2b) or PUVA plus retinoid combinations can be used (4, 6). In our study, four MF patients were treated with PUVA plus IFN-α2b and two MF patients were treated with PUVA plus retinoid combinations.

Data regarding phototherapy in SPP and LLP have been obtained from small case series or case reports while no randomized studies or observational studies are present. Optimal treatment duration has not been established (3). In a study evaluating standardization of NB-UVB and PUVA regimens in early stage MF, data were pooled from 3 studies on NB-UVB. In that study, it was found that complete remission rate was 69.1% while relapse rate was 39.3% and mean time from complete remission to relapse was 8 months in patients underwent NB-UVB therapy. In the same study, data were pooled from 12 studies on PUVA. It was found that complete remission rate was 79.5% while relapse rate was 59% and mean time from remission to relapse was 13 months in patients underwent PUVA therapy (7). In a retrospective study, Ponte et al. compared PUVA and NB-UVB therapies in patients with MF. Authors found complete remission rate of 62.1% by PUVA and 68.4% by NB-UVB; however, no significant difference was found in time to relapse between PUVA and NB-UVB (11.5 and 14 months, respectively) (8). In the study by Ahmad et al., it was reported that complete remission rate was 64% for PUVA and 50% for NB-UVB while time to relapse was 10 months for PUVA and 11.5 months for NB-UVB (9). In the study by Diederan et al., there was no significant difference in complete remission rate and mean time to relapse in early stage MF between PUVA and NB-UVB (10). In their study, Unal et al. evaluated PUVA and NB-UVB therapies in 61 patients with MF. Authors reported that complete remission rate was 84.6% for PUVA and 71.4% for NB-UVB. They also found that number of sessions and duration to achieve complete remission were significantly higher in patients underwent PUVA while cumulative dose was 202.3 J/cm^2 for PUVA and 58.2 J/cm^2 for NB-UVB (11).

There is no consensus whether maintenance therapy should be given in MF. In 2015 guidelines on safe and effective use of PUVA therapy by British Photodermatology group, it has been suggested that maintenance PUVA therapy can be recommended to prevent rapid relapse in MF patients (level of evidence: experience and formal consensus of group) (12). However, Sánchez MA and Hernández et al. reported that maintenance PUVA therapy failed to prevent recurrence in MF patients (13, 14). Larger, randomized, clinical trials are needed to establish a standardized treatment protocol in early stage MF and to determine whether maintenance therapy is essential. In a study on 62 patients with parapsoriasis, Duarte

et al. reported similar complete remission rates for PUVA (91.1%) and NB-UVB (82.3%) (15). In their study, Herzinger et al. treated 18 patients with SPP by NB-UVB. Mean number of NB-UVB sessions was 32.8 and mean cumulative dose was 35.45 J/cm^2. Authors reported that mean time from complete remission to relapse was 29 weeks (16). In a study on 45 patients with SPP, Aydogan et al. reported that complete remission rate was 73.3% and mean cumulative dose was 14.3 J/cm^2 with NB-UVB therapy. Authors also reported that mean number of sessions was 29 and that relapse occurred in 6 patients while mean time from complete remission to relapse was 7.5 months(17). Similar results with our study were reported in previous studies evaluating effectiveness of NB-UVB and PUVA therapies in early stage MF and parapsoriasis. In our study, it was found that higher number, duration and dose of PUVA therapy was required to achieve complete remission in patients with early stage MF when compared to those with parapsoriasis. In addition, it was also found that duration of NB-UVB, number of sessions and duration required for complete remission were significantly higher in patients with LPP than those with SPP. In our study, it was seen that NB-UVB and PUVA doses to achieve complete remission was higher than those reported in the literature were.

We observed that NB-UVB was as successful as PUVA in the treatment of SPP and LPP. However, it was concluded that choosing PUVA therapy preferentially will be more appropriate in MF. Our study contributes to literature by sharing phototherapy data in the treatment of these disorders.

Conflict of Interests

The authors declared no conflict of interest with the present article.

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