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Fototerapia como Primeira Linha Terapêutica para a Micose Fungóide: Um Estudo Retrospetivo de 10 Anos

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RESUMO – **Introdução**: A fototerapia, em particular a fotoquimioterapia com psoralenos associados a radiações ultravioleta do tipo A (PUVA) e a fototerapia com radiações ultravioleta do tipo B de banda estreita (nbUVB), é um dos pilares do tratamento da micose fungóide (MF). **Métodos**: Foram analisados os resultados de doentes com MF que fizeram tratamento de primeira linha com PUVA ou nbUVB na Unidade de Fotodermatologia do Serviço de Dermatologia do Centro Hospitalar Universitário do Porto, de 2007 a 2017. O resultado primário foi a resposta ao tratamento. O resultado secundário foi a sobrevida livre de recidiva. **Resultados**: De um total de 34 doentes com MF, nove (26,5%) foram diagnosticados no estadio IA e 25 (73,5%) no estadio IB. Destes doentes, 30 (88,2%) foram tratados com PUVA e quatro (11,8%) com nbUVB. Globalmente, 24 (80%) doentes tratados com PUVA e dois (50%) doentes tratados com nbUVB tiveram respostas completas. Foi observada recidiva em 17 (70,8%) doentes tratados com PUVA e em dois (100%) doentes tratados com nbUVB. A mediana da sobrevida livre de recidiva foi de 12 meses para o grupo PUVA e 6 meses para o grupo nbUVB. **Conclusão**: A fotoquimioterapia com PUVA é uma terapêutica eficaz na MF em estadios precoces. O UVB de banda estreita pode ser uma alternativa terapêutica válida para estes doentes. Todavia, a amostra reduzida do grupo nbUVB neste estudo limita as conclusões sobre a sua eficácia.
PALAVRAS-CHAVE – Fármacos Fotossensibilizantes; Fototerapia; Micose Fungóide/tratamento; Terapia PUVA.

Phototherapy as a First Line Treatment for Mycosis Fungoides: A 10-year Retrospective Study

ABSTRACT – ***Introduction:*** *Phototherapy, particularly psoralen plus ultraviolet A (PUVA) and narrowband ultraviolet B (nbUVB), is a mainstay in the treatment of Mycosis Fungoides (MF).* ***Methods:*** *We analyzed outcomes of MF patients treated for the first time with either PUVA or nbUVB at the Photodermatology Unit, in the Department of Dermatology of Centro Hospitalar Universitário do Porto, from 2007 to 2017. The primary outcome was response to treatment. The secondary outcome was disease relapse free survival.* ***Results:*** *From a total number of 34 patients with MF identified, nine (26.5%) patients were diagnosed at stage IA and 25 (73.5%) patients were diagnosed at stage IB. Of these patients, 30 (88.2%) were treated with PUVA and four (11.8%) with nbUVB. Overall, 24 (80%) patients treated with PUVA and two (50%) patients treated with nbUVB had complete responses (CR). Relapse was observed in 17 (70.8%) PUVA treated patients and two (100%) nbUVB treated patients. Median disease relapse free survival was 12 months for PUVA and 6 months for nbUVB.* ***Conclusion:*** *PUVA is an effective therapy in early MF. Narrowband UVB could be a valid therapeutic alternative for these patients. However, the small size of nbUVB group in our study limits the conclusions about its efficacy.*
KEYWORDS – *Mycosis Fungoides/therapy; PUVA Therapy; Photosensitizing Agents; Phototherapy.*

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INTRODUCTION

Primary cutaneous lymphomas are defined as non-Hodgkin lymphomas present in the skin without evidence of extracutaneous disease at the time of diagnosis.[1] In the western world, cutaneous T cell lymphomas (CTCL) account to about 75% to 80% of all primary cutaneous lymphomas. Mycosis fungoides (MF) is the most common type of CTCL, with 75% of affected patients being at early stage during initial diagnosis.[2,3]

Skin-directed therapies, including phototherapy, are a mainstay treatment for most patients with early stage MF.[4] Both narrow-band ultraviolet B light (nbUVB) phototherapy and psoralen plus ultraviolet A light (PUVA) photochemotherapy, have recognized efficacy in MF and are widely used treatments for early stages.[5]

Despite the large use of phototherapy on early stage MF, exact mechanisms of action are currently unknown. The primary direct effects of UVB are on cell population localized in the epidermis and the upper dermis. The hypothesized mechanisms of action of nbUVB on MF include apoptosis of keratinocytes and infiltrating lymphocytes, inhibition of keratinocyte growth rate and lowered production of pro-inflammatory cytokines in lesion's microenvironment and increased production of anti-inflammatory cytokine.[6] The theoretical advantages of PUVA over nbUVB are in terms of reduced erythemogenic activity and better penetration towards deeper dermal layers, up to hypodermis and deepest adnexal structures, where can affect lymphocytes as well as other resident skin cells, such as fibroblasts, dendritic cells, mast cells, endothelial cells or macrophages.[5,6]

We conducted a retrospective study to evaluate the efficacy of phototherapy, particularly PUVA and nbUVB, in early stage MF, in a tertiary hospital of Porto, Portugal.

METHODS

Study design and population

We retrospectively reviewed all patients treated with phototherapy for MF at the Photodermatology Unit, in the Department of Dermatology of Centro Hospitalar Universitário do Porto, in a 10-year time period (from 2007 to 2017). The cohort included all patients with early-stage MF who had been treated for the first time with either PUVA or nbUVB.

All patients had stage IA or IB disease. The stage of the disease was determined according to the TNMB classification by the International Society for Cutaneous Lymphoma and Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC).[3]

Patients with more advanced stages of MF, other types of cutaneous T-cell lymphoma, patients who received any concurrent treatments (e.g. interferon, acitretin, etc.) or with missing data pertaining to the primary study outcome were excluded in the study population.

Patient's medical records were reviewed, and demographic (gender and age) and clinical data (phototype, disease duration, response, side effects and treatment protocols) were collected.

Phototherapy treatment protocol

Both PUVA and nbUVB are used to treat MF. Physicians determine treatment type based on patient's comorbidities, disease stage and type of skin lesions (patches versus plaques). Phototherapy was the only treatment for all cases included in this analysis, and no other systemic treatment was applied during the observation period.

Phototherapy sessions were carried out two times per week. Concerning PUVA treatment, 8-methoxypsoralen 0.6 mg/kg was administered two hours prior to therapy session. The initial UVA doses were calculated according to each patient's skin type (I, 0.5 J/cm^2; II, 1 J/cm^2; III, 1.5 J/cm^2; IV, 2 J/cm^2). Fixed dosage increments during therapy were also consistent with skin phototype ((40% of previous dose or 20% if patients developed erythema during treatment). Concerning nbUVB, the starting dose (I and II, 0.1 J/cm^2; III e IV, 0.2 J/cm^2). and dosage increments (20% of previous dose or 10% if patients developed erythema during treatment) were adjusted to the skin type. PUVA and nbUVB treatment were continued until complete skin clearance or no further clinical improvement was noted. Patients were not submitted to a maintenance regimen.

Outcomes

The primary outcome was response to treatment achieved by patients who received PUVA and nbUVB treatment. The secondary outcome was disease relapse free survival in PUVA treated and nbUVB treated patients.

Responses were defined according to the consensus statement of the International Society for Cutaneous Lymphomas (ISCL) as follows: complete response (CR), complete clearance of all skin lesions; partial response (PR) with >50% remission of skin lesions; no response (NR), any clinical result less than a PR; disease progression, ≥ 25% increase in skin disease from baseline or development of new tumors (T3) in patients with T1, T2 or T4 with only skin involvement; relapse, any clinically significant disease reemergence requiring further treatment.[7]

Disease relapse free survival was defined as time from treatment completion to clinically significant disease reemergence requiring further treatment.

Statistical analysis

The small sample size did not allow a comparative analysis between the PUVA-treated group and the nbUVB--treated group nor the identification of variables predicting relapse. Kaplan–Meier analysis was performed to plot relapse-free rates after phototherapy modalities.

All analyses were performed using the IBM SPSS Statistics 24.0 (SPSS, Chicago, IL, USA).

RESULTS

Patient Characteristics

Thirty-four patients with early stage MF, fourteen females (41.2%) and 20 males (58.8%), were included. Thirty cases (88.2%) were treated with PUVA, while four (11.8%)

Table 1 - Patient clinical characteristics.

CLINICAL CHARACTERISTICS		PHOTOTHERAPY GROUP	
		nbUVB (n=4)	PUVA (n=30)
Gender, n (%)	Females Males	1 (25) 3 (75)	13 (43) 17 (57)
Age at diagnosis (years)*		57 (27-63)	59 (29-79)
Phototype, n (%)	I II III	0 (0) 0 (0) 4 (100)	3 (10) 12 (40) 15 (50)
Stage, n (%)	IA IB	1 (25) 3 (75)	8 (27) 22 (73)

N= number of patients; nbUVB= narrowband ultraviolet-B light phototherapy; PUVA= psoralen plus ultraviolet A light phototherapy.
* Results are presented as median and (minimum-maximum) values.

received nbUVB. The median age at diagnosis was 59 years in the PUVA group and 57 years in the nbUVB group. All patients had stage IA or IB disease. In PUVA group, eight patients (27%) had stage IA MF and 22 patients (73%) had stage IB MF. In the nbUVB group, one patient (25%) had stage IA MF and three patients (75%) had stage IB MF. Table 1 summarizes patients' clinical data.

Treatment outcome

Overall, 24 patients (80%) of the PUVA group and two patients (50%) of the nbUVB group achieved CR (Fig. 1). In PUVA group, four patients (13.4%) discontinued treatment, two of them (6.7%) due to adverse reactions and another two patients (6.7%) because of several missed sessions. In nbUVB group, one patient (25%) suspended phototherapy due to an adverse event and another patient (25%) due to several missed sessions.

Median number of treatment sessions to achieve complete response was of 30 for PUVA and of 23 for nbUVB. Median irradiation dose was 270.4 J/cm2 for PUVA and 16.3 J/cm^2 for nbUVB.

Disease relapse was observed in 17 out of 24 patients with CR (70.8%) treated with PUVA group (follow-up between 3 and 108 months) and in two out of two patients with CR (100%) treated with nbUVB group. The median disease-free survival (DFS) was 12 months (range 4-35) in PUVA group and 6 months (range 3-8) in nbUVB group (Fig. 2). Relapse-free rate at 1 year was 53% in PUVA group and 100% in nbUVB group.

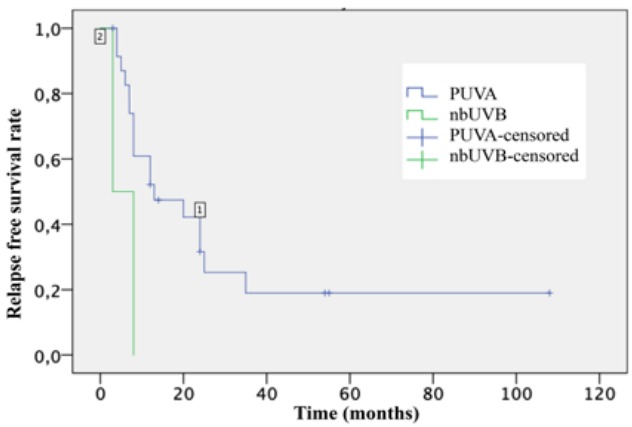

Figure 2 - Kaplan–Meier analysis of disease relapse free survival after first PUVA or nbUVB treatments.

Ten patients had at least one more round of PUVA therapy after disease relapse. Two of those had to have PUVA treatment stopped early for personal reasons. The remaining eight patients responded completely to the second round of PUVA therapy. Disease relapse was observed in

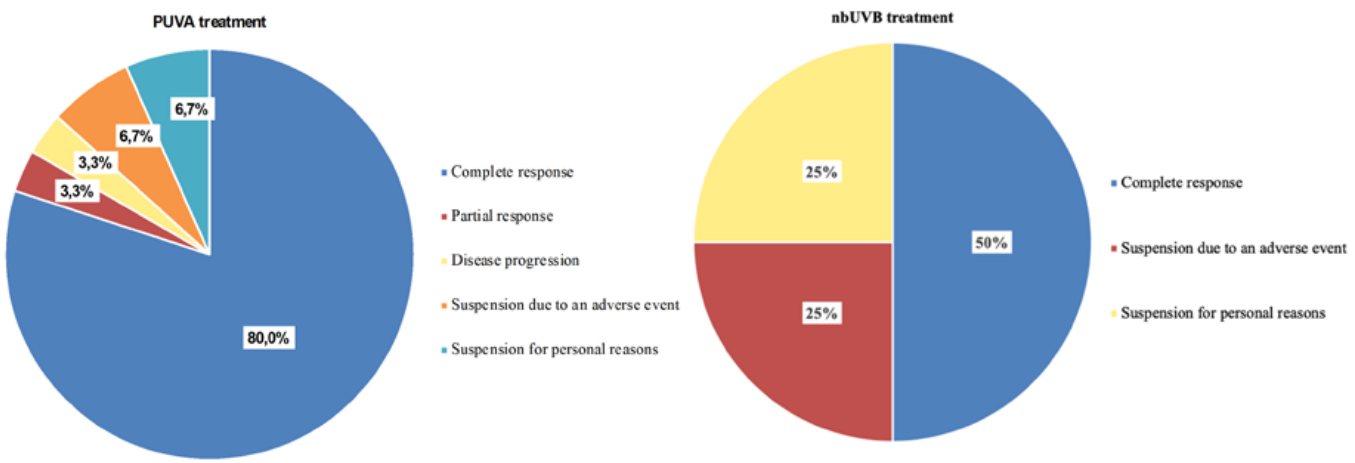

Figure 1 - Response to treatment achieved by patients who received PUVA and nbUVB treatment.

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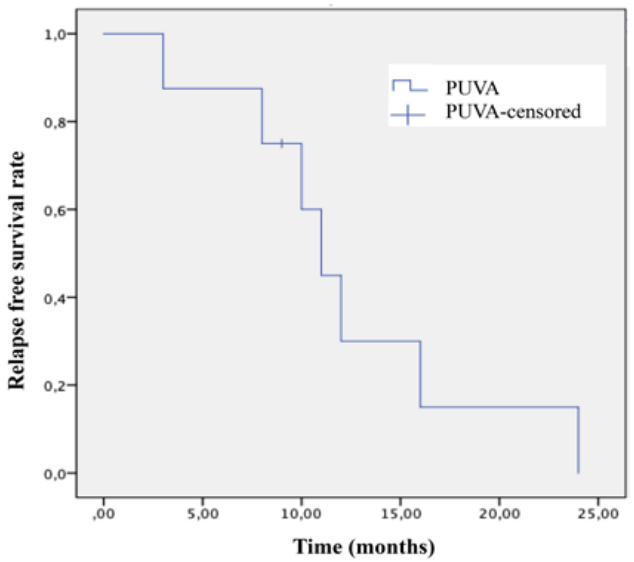

Figure 3 - Kaplan–Meier analysis of disease relapse free survival after a second round of PUVA after disease relapse.

seven out of eight patients who had a CR after the second round of PUVA. The mean time to relapse was 11 months (range 3-24) (Fig. 3).

Safety

Regarding PUVA-induced toxicities, two patients reported erythema and one patient report pruritus. Among these patients, two discontinued treatment due to side effects' severity. In nbUVB group, one patient stopped therapy due to polymorphous light eruption.

DISCUSSION

The first publication on the use of PUVA phototherapy for the treatment of MF was in 1976,[8] and since then, more than 30 studies of treatment with PUVA in patients with MF have been published in English. It is difficult to compare results of the reports because there were differences in treatment protocols for the clearance and maintenance phases, heterogeneity of the quality of studies, sample size or patient selection and differences in outcome measures, relapse definition or definition of time of relapse.[5]

Our experience with this series of 30 patients confirms the efficacy and safety of treatment with PUVA in patients with stage IA and IB MF. Overall, 80% of patients treated with PUVA achieved CR and 3.3% of patients achieved PR. These findings are in accordance with other studies, that reported PUVA-induced CR rates between 62%-92%.[9-14] In a Portuguese study published by Ponte *et al*, PUVA treatment led to CR in 62.1% of the patients.[12] The relapse rate ranged from 36% to 92% in recent studies, with a mean relapse-free interval ranging from 12 to 57 months. Our results showed a relapse rate of 71%, with a median relapse-free interval of 12 months. These results are in accordance with Ponte and colleagues, who reported a relapse rate of 90% after PUVA, with a mean relapse-free interval of 12 months.[12]

Narrowband UVB has been used since at least 1999 for the treatment of MF.[15] Our nbUVB group is smaller (four patients) than most of the published groups, with samples ranging from 14 to 109 patients.[9,12,14,16-24] In our series, nbUVB led to CR in 50% of patients, with a median relapse--free interval of 6 months. However, the small size of nbUVB group limits the interpretation of these results. Other published studies, reported CR rates between 54% - 91%, relapse rates ranged from 5% to 83%, with a mean relapse-free interval ranging from 5 to 26 months.[9,12,14,16-24]

Data about the efficacy of a second course of phototherapy after MF relapse is limited. Abel *et al* reported a CR in 50% of the patients (n=6) after a second clearing phase of PUVA therapy. Disease relapse was observed in all patients with CR after the second course of PUVA.[25] Querfeld *et al* reported that most of patients responded again when PUVA treatment was resumed more intensively after disease relapse, and 36% of relapse patients remained disease free at last follow-up.[26] Wackernagel *et al* observed a CR in seven of 10 (70%) patients who received a second round of PUVA therapy after disease relapse. Disease relapse was reported in six of seven (86%) patients after the second successful course of PUVA; the mean time to relapse was 11 months.[11] In contrast to these three studies, our PUVA treatment protocol did not include a maintenance regimen. Still, we found similar results, with eight of 10 (80%) patients achieving CR after the second round of PUVA therapy. The disease relapse rate was 88% after the second course of phototherapy, with a mean time to relapse of 11 months.

The present study was limited by the small number of patients included and by its observational and retrospective design.

Narrowband UVB is a valid therapeutic option in early stage MF and several studies demonstrated no difference between PUVA and nbUVB in early stage MF in terms of responses and time to relapse, but the results from these studies are difficult to compare.[6] In addition, a recent large retrospective study showed that PUVA treatment results in better response rates and longer relapse-free intervals in both patch and plaque stage, compared to nbUVB treatment.[14] Still, the small size of nbUVB group limits the conclusions about its efficacy and comparison with PUVA efficacy. Therefore, there is an unmet need for a prospective, randomized, controlled study to compare the efficacy of both modalities of phototherapy and to clarify other specific issues, namely the impact of the maintenance protocol on the outcome and the relapse rates once long-term maintenance is stopped.

In conclusion, although our study was limited by the small number of patients included, and by its observational and retrospective design, the results obtained are in accordance with previous publications about the efficacy and safety of PUVA treatment in stage IA and IB MF.

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