Diplomarbeit

A prospective cross-over comparison between narrowband UVB (311nm) and PUVA therapy for the treatment of patch-stage mycosis fungoides.

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Priv. Doz. Dr. Wolf Ingrid

Ort, Datum …….. (Unterschrift)

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resource, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, …… *Anastasija Sugic*

Preface

Aus Gründen des internationalen Wissenschaftsaustausches, des ständigen Wissenswachstums in der Medizin und meiner persönlicher Sprachenwicklung, entschloss ich mich meine Diplomarbeit in englischer Sprache zu erstellen.

Due to the international knowledge interchange, to constant medical background increase and to my personal language development I decided to write my diploma thesis in English.

I grew up in a small town called Celinac, in Bosnia and Herzegowina. My childhood was affected by the war in 1991. During the war I felt the need to help injured people as much as I could. I finished my high school education and the medical school for nursing in Banja Luka, thereafter I came to study at the Medical University of Graz. After learning German I started to get some basic medical theoretic and practical knowledge and decided to participate an internship in South Africa. I was at the department of dermatology in Groote Schuur Hospital, Cape Town, where I have discovered my interests for skin disorders. I further developed my interests in dermatology at the department of dermatology at the phototherapy division in Graz. I was able to join a project started by Prof. Dr. Hofer about therapy comparison between narrowband UVB (311nm) and PUVA therapy for the treatment of patch-stage mycosis fungoides. I have had the opportunity to assist during the follow-up examination, and I was able to develop my communication skills with patients, I summarized the data collected by the phototherapy division during this prospective study and I have learned some basics in statistical data analysis. The first results of this project were presented as a poster at the International 7th EADV Spring Symposium, Cavtat, Croatia, May 13-16, 2010. Subsequently, I decided to summate all my experiences collected during my assistance and to write my diploma thesis about this topic.

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I want to express my most sincere acknowledgments to Prof. Dr. Angelika Hofer who gave me the opportunity to expand my clinical experience and supported me during the writing of my thesis at the department of dermatology in LKH Graz. I would like to thank Doz. Dr. Ingrid Wolf for her support as supervising tutor.

Special acknowledgments go to the department of phototherapy for clinical assistance and collecting study data. Many thanks to Mr. Quehenberger for his statistical analysis support.

I want to thank my parents, brother, partner Rene, and all my friends for giving me encouragement during my studies in Graz. Their love has been truly inspiring and motivating to me.

Zusammenfassung

UVB 311 nm Therapie versus PUVA Therapie bei Patienten mit Mycosis fungoides im Frühstadium.

Einleitung: Die Mykosis fungoides (MF) wird als Proliferation maligner T-Helferzellen definiert und stellt die häufigste Form der primär kutanen T-Zell-Lymphome dar. Die Erkrankung betrifft Patienten im Alter ab 40 Jahren und zeigt eine Tendenz für männliches Geschlecht. Die Erkrankung beginnt mit untypischen, schuppenden patch-artigen Effloreszenzen, die leicht jucken. Nach Jahren können sich plaque-artige, leicht erhabene Effloreszenzen bilden. Auch eine Ausbreitung auf die ganze Haut (Erythrodermie) ist möglich. Im Rahmen der Progression bilden sich multiple, rot-bräunliche Tumorknoten der Haut die oft ulzerieren. Die MF kann nach Jahren auch Lymphknoten und innere Organen befallen.

Für das Frühstadium der MF (inkludiert Stadium IA, IB und IIA) stehen verschiedene Therapieoptionen wie eine topische Therapie mit Steroiden, Lichttherapie oder die systemische Behandlung mit Retinoiden, Kortikoiden, Carmustine, Bexarotene, sowie Interferon-alpha zur Verfügung.

Bei ausgedehntem Befall oder fehlendem Ansprechen auf die topische Therapie kommt eine Lichttherapie zum Einsatz. Die Therapie der 1. Wahl war hier lange Zeit die Photochemotherapie (Psolaren plus Ultraviolet A- PUVA), welche schon seit mehr als 30 Jahren bei Frühstadien in der MF-Therapie etabliert ist. Die Nebenwirkungen wie generalisierte Photosensibilität, Übelkeit, Erbrechen und das Risiko der Photokanzerogenität sind nicht zu ignorieren.

Seit 1999 wird die Schmalband UVB Therapie (NB-UVB 311 nm) erfolgreich zur Behandlung der MF im Frühstadium eingesetzt und zeichnet sich durch geringere Nebenwirkungen aus.

Frühre retrospektive Studien gaben Hinweise dafür, dass die beiden Phototherapien gleichermaßen effektiv sind. Einschränkend muss aber gesagt werden, dass viele dieser Arbeiten Kombinationstherapien im weiteren Verlauf verwendet hatten, uneinheitliche Therapieregime oder Erhaltungstherapie zur Anwendung kamen. Außerdem zeigen diese Studien keine ausreichenden Angaben, mit welchen der beiden Lichtherapien die bessere Langzeitergebnisse erziehlt werden können.

Ziel: Das Ziel unserer prospektiven Studie war die Ansprechrate und die Rezidiv-freien-Intervalle nach NB-UVB beziehnugsweise PUVA Therapie bei Patienten im Frühstadium der Mykosis fungoides zu vergleichen.

Material und Methoden: 18 Patienten (6 Frauen, 12 Männer; Durchschnittsalter: 64 Jahre) mit klinisch und histologisch bestätigter MF (Stadium IA und IB) wurden zwischen 2000 und 2009 in diese prospektive Cross-Over Studie eingeschlossen. Die randomisierten Patienten wurden dreimal wöchentlich entweder mit NB-UVB oder mit PUVA behandelt. Die Behandlung wurde für mindestens acht Wochen fortgeführt, und nach Abheilung der Läsionen (zumindest > 95% Läsionsfreiheit der Haut), beendet. Wenn es nach der ersten Therapie zu einem Rezidiv (> 3% Körperöberflache) kam, wurde der Patient mit der jeweils anderen Lichtherapie behandelt.

Resultate: 6 Patienten (33%) die nur mit einem Therpieregime behandelt werden, zeigten keine Rezidive. 12 Patienten (67%) hatten nach der erste Therapie ein Rezidiv und wurden anschließend mit der zweite Therapie behandelt (Cross-Over Patienten). Alle 12 Patienten, die eine zweite Therapie erhielten, entwickelten neuerlich im Follow-up Intervall ein Rezidiv. Insgesamt fanden 16 NB-UVB und 14 PUVA Behandlungen statt. Es bestand kein signifikanter Unterschied zwischen der NB-UVB und PUVA Therapie im Bezug auf die Therapiezahl und die durchschnittliche Therapiedauer. Alle Patienten erreichten eine weitgehende Abheilung der Hautläsionen. Die Rezidiv-freien-Intervalle nach NB-UVB beziehungsweise PUVA Therapie zeigten keinen signifikanten Unterschied zwischen beiden Therapien (p=0.66). Das mediane Rezidiv-freie-Intervall war 12 Monate nach dem ersten Therapiezyklus (Beobachtungsperiode 1) und 8 Monate nach dem zweiten Therapiezyklus (Beobachtungsperiode 2); (p=0.019). Das Stadium der Erkrankung war ein signifikanter Risikofaktor für das Auftreten eines Rezidivs. Die Zahl der Nebenwirkungen war niedriger unter NB-UVB Therapie im Vergleich zur PUVA Therapie.

Zusammenfassung: NB-UVB und PUVA Therapie zeigen sich als gleichwertige Therapieoptionen im Frühstadium der MF (Stadium IA und IB) im Bezug auf die Ansprechrate und die Länge der Rezidiv-freien-Intervalle.

Abstract

A prospective cross-over comparison between narrowband UVB (311nm) and PUVA therapy for the treatment of patch-stage mycosis fungoides.

Introduction: Narrowband ultraviolet B (NB-UVB) has been reported to clear patch-stage mycosis fungoides (MF) with fewer side effects compared to psoralen plus long-wave ultraviolet A (PUVA) therapy. However, particularly for patients with early-stage MF, it remains unclear which phototherapy provides the best outcome.

Objectives: The aim of the present study was to compare the primary response rate and the relapse-free intervals after the treatment of patch-stage MF with NB-UVB and PUVA.

Method: Between 2000 and 2009 eighteen Caucasians (6 women, 12 men; mean age: 64 years) with clinically and histologically confirmed patch-stage MF (stage IA and IB) were enrolled in this prospective cross-over study. Patients were treated 3 times per week with either NB-UVB or PUVA and treatment was stopped as soon as skin lesions had cleared. Those patients, who relapsed after the first phototherapy regimen, were then treated with the other phototherapy regimen. The relapse-free interval in follow-up period 1 after the first treatment regimen (NB-UVB or PUVA) and in follow-up period 2 after the second treatment regiment (PUVA or NB-UVB) was observed and compared. Relapse-free intervals after all NB-UVB and PUVA treatments were also analysed.

Results: All patients cleared (with more than 95% resolution of skin lesions) at the end of each treatment regimen. No significant difference was detected between the treatments in terms of number of treatments, mean treatment duration and irradiation dose. Six (33%) patients were treated with a single treatment (NB-UVB or PUVA), because they did not show a relapse within the study observation period. Whereas 12 (67%) patients relapsed after the first treatment regimen and therefore received both NB-UVB and PUVA therapy (cross-over patients). Overall, 16 patients with NB-UVB treatments and 14 patients with PUVA treatments were analysed. The relapse-free intervals were not statistically significant (p=0.66) between the two treatment modalities. The median relapse-free interval was 12 months after the first treatment regimen with NB-UVB or PUVA and 8

months after the second treatment regimen with PUVA or NB-UVB (p=0.019). Disease stage was a significant risk factor for relapse. The number of side effects was lower in the NB-UVB treated group compared to the PUVA group.

Conclusion: NB-UVB and PUVA seem to be equal treatment modalities for patch-stage MF (IA and IB) in relation to clearing of lesion and relapse-free interval.

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1 INTRODUCTION

Mycosis fungoides (MF) is the most frequent form of cutaneous T-cell lymphoma (CTCL) in which the malignant clone of T-helper lymphocytes affects the skin as primary site (1). As a heterogeneous group of non-Hodgkin lymphomas (NHL), CTCL stands out by its initial skin involvement and should be separated from other NHL with skin involvement such as peripheral T-cell lymphomas and adult T-cell leukemia or lymphoma. It has recently been found that the MF age-adjusted incidence rate was 4.1/1 000 000 persons in the United States. Black people have higher incidences than white people and men are more frequently affected than women (1, 2, 3).

MF was first described in 1806 by Alibert (4) with primary skin involvement and slow progression in the early-stages. Typical lesions are limited patches which may progress after various time periods into generalized patches, plaques or cutaneous tumors with dissemination to the lymph nodes and visceral organs (5, 6). An erythrodermic variant of MF is the Sezary syndrome (SS) showing the presence of tumor cells circulating in peripheral blood. In most cases Sezary syndrome is mentioned with MF, but it is a separate entity according to the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)-World Health Organisation (WHO) classification (2). Only 4% of the CTCL patients have Sezary syndrome and its clinical presentation is different with worse prognosis compared to MF (19).

1.1 Aetiology

The aetiology of CTCL including MF still remains unsolved. There are theories supporting the believe that CTCL is associated with human T-cell lymphotropic virus I/II (HTLV-I/II) as known for T-cell leukemia in which HTLV-I virus infection is playing a pathogenic role (7). HTLV-I virus was directly isolated from patient biopsies, who was supposed to have CTCL, but later on he developed adult T-cell lymphoma/leukemia (8). Until now, no study was able to confirm a virus in biopsies of patients with CTCL (9).

Another long time established theory associated with the development of MF was that antigen persistence could induce chronic stimulation of lymphocytes and possible transformation into low-grade malignant T-cell lymphoma (10). However, a responsible antigen for transformation of T-cell lymphocytes could not be defined. Therefore it was assumed that the exposure to substances, which are used in the chemical, textile or metal industry, might be responsible for the increased incidence of allergies, fungal and viral infections in patients with CTCL compared to healthy controls (11). One recent report found no significant relation between job-related or environmental exposure and immune response; however a higher prevalence of non-lymphoma cutaneous malignant disorders in MF patients compared to a healthy group was demonstrated (12).

1.2 Pathology and Immunology

Early pathological markers of MF show a dominance of small, hyperchromatic lymphoid cells with a tendency to infiltrate the epidermis. During disease progression a selective colonisation of the epidermis with cerebriform atypical lymphocytes can be observed. Invasion with atypical lymphocyte clusters, known as Pautrier microabscesses, is a typical sing of the florid lesion. This pattern is called phenomenon of epidermotropism (Fig.1). In early-stage MF the number of plasma cells or eosinophils may be elevated, but when the infiltrate becomes more epidermotropic, there is only a pure T-cell population left. Lesions with epidermotropism may be associated with moderate spongiosis in early MF (13).

Most patients develop monoclonal malignant T-cell clones with a majority of CD4 positive and reactive CD8 positive T-cells lymphocyte with Th1 cytokine (IFN-gamma, IL-2 and IL-12) dominance in early-stage lesion of MF. In advanced stages of the disease it comes to an increase of malignant CD4+ cells, non-malignant CD8+ reduction and dominance of Th2 cytokine (IL-4, IL-5, IL-10 und IL-13). These changes are therapy targets of the biologic immune modifiers such as IFN-alpha, IFN- gamma or IL-12 with function to stimulate Th1 cytokines and regulate immune response (14).

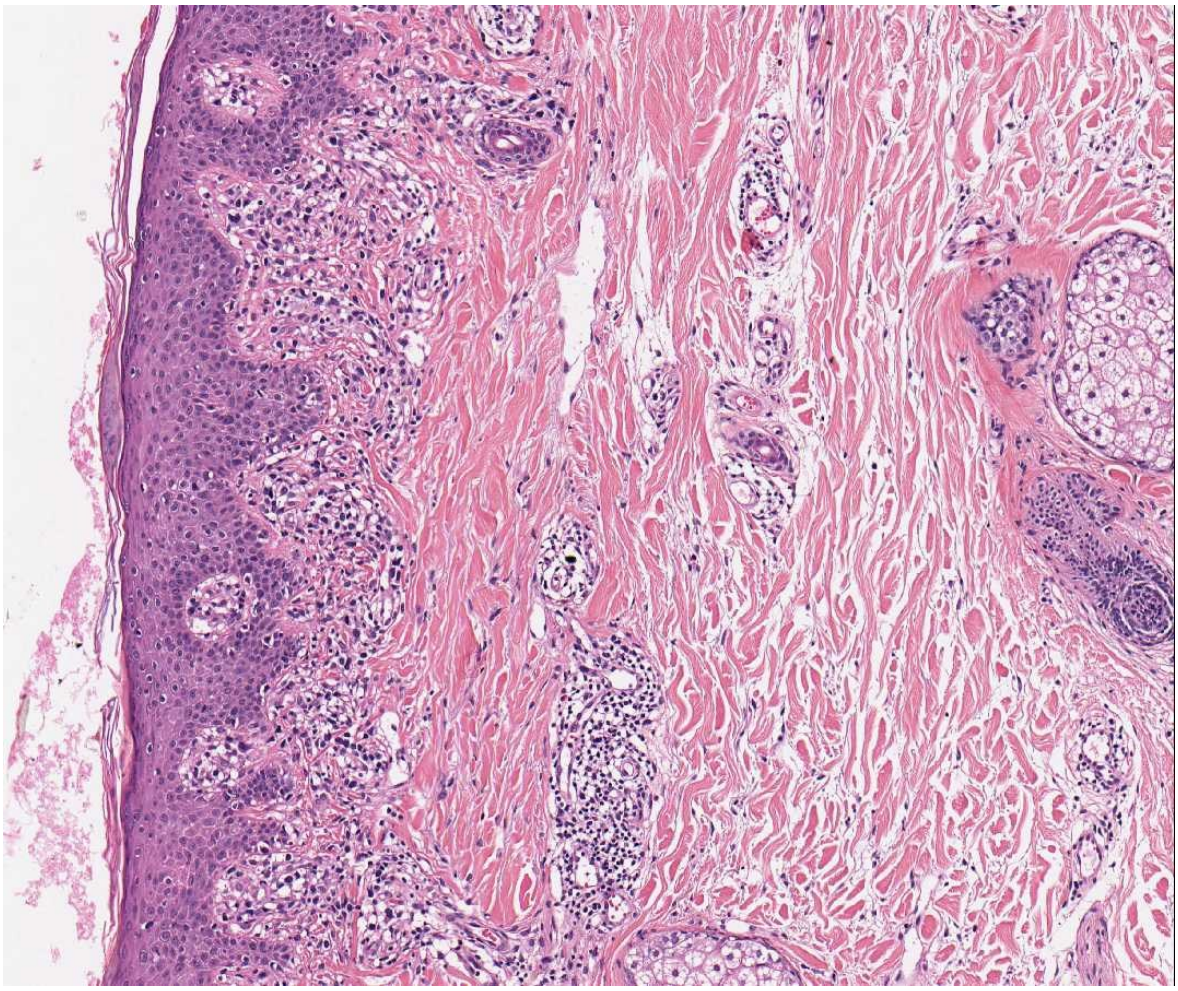

Fig.1 Histology of early-stage mycosis fungoides showing epidermotropism with atypical T-lymphocytes

1.3 Differential diagnosis (13)

The differentiation of early-stage MF from other skin conditions such as contact dermatitis, fungal infection, arthropod bites and lymphomatous drug eruptions can be challenging and demands good correlation of pathological features with clinical lesions. A biopsy should be considered in every patient having pruritic plaques that do not clear with local therapy. A contact dermatitis can show more spongiosis in histology compared to MF. Fungal infection can be ruled out by Woods light or mycological examination. Arthropod skin bites might have more eosinophils in the dermis than MF. Lymphomatous drug eruptions attendant to infiltrate more the vesicular surrounding area compared to MF (13).

Sometimes it is very delicate to have clear pathological confirmation of suspected clinical lesions and repeated series of biopsies, every three to six months, may give a reliable diagnosis of the disease.

A recently published report (15) investigated genes that are expressed in early-stage MF and associated with inflammation, immune activation and apoptosis regulation processes. Two genes have been described (TOX and PDCD1), which were significantly up-regulated in genes biopsies of early-stage MF lesions. Those genes, especially TOX, could be currently specific molecular markers for histological diagnosis of early-stage MF.

High sensitive techniques, such as polymerase chain reaction (PCR) and single strand conformational polymorphism (SSCP), can identify monoclonal band rearrangement in a small number of T-cell-receptor genes. Due to the high sensitivity of this technique other rearranged bands of monoclonal proliferation in benign diseases, such as contact dermatitis and psoriasis, may also be identified. Thus, identification of T-cell-receptor rearrangement should be in correlation with pathological and clinical characteristics. The presence or absence of this rearrangement may be of value for prognosis and therapy response in patients with different stages disease, but more studies are needed (16).

1.4 Clinical characteristics (1,2,5,6,13)

Classical early-stage of MF appears with small erythematous, pruritic patches mostly on the trunk, breasts and buttocks. The lesion may show atrophy and fine scaling which may difficult to differentiate to pityriasis rosea, fungal infection, atopic dermatitis, allergic contact dermatitis or psoriasis. In progressive disease, lesions may become more distinct erythematous plaques dominating the trunk rather than face, neck or extremities. The plaques vary in size (small to large) with slight scaling and irregular borders. Limited-plaque MF is defined as less than 10% involvement of the body surface and extensive-plaque MF is defined as more than 10% of the body surface involvement. In the more progressive stage of the disease patients can develop nodules and ulceration with or without pain and secondary infection.

Life expectancy of patients in early-stage MF is not different from age-matched healthy controls. However, 30% of patients progress to extracutaneous involvement with poor prognosis (19).

There are various forms of MF, which are sometimes difficult to differentiate from other aggressive CTCL, especially if they progress rapidly.

The tumeur d'emblee form of MF is characterized by a rapid development of nodes without any patch or plaque lesions.

A more common variant of MF is the erythrodermic type with a quick onset of erythroderma, a tendency to develop lymphadenophathy and involving peripheral blood. Palms and soles show hyperkeratotic skin involvement and severe scaling.

The poikilodermatous form is characterized by widespread poikiloderma usually on the trunk, but less common on the breast or buttocks. This form may present hyper- or hypopigmentation and atrophy with burning sensations rather than itching.

1.5 Staging

In 1979 Bunn and Lamberg (17) first published a staging system for MF. It has been proven to be useful for clinical use and remained until lately to be the standard for clinical reports. A recently revised staging system was suggested by the International Society for Cutaneous Lymphoma and the Cutaneous Lymphoma Task Force of the EORTC (18) (Table 1 and 2); it was validated in a large cohort from the United Kingdom (19).

Table 1. Staging classification based on the updated tumor-node-metastasis-blood (TNMB) staging as recommended by the ISCL/EORTC (18)

	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2	0	0, 1
IIB	3	0-2	0	0, 1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

ISCL, International Society for Cutaneous Lymphoma;
EORTC, European Organization for the Research and Treatment of Cancer.

Table 2. Tumor-node-metastasis-blood (TNMB) staging as recommended by the ISCL/EORTC (18)

Skin

T1 -Limited patches, papules, and/or plaques covering less than 10% of the skin surface

T2 -Patches, papules, or plaques covering more than 10% of the skin surface

T3 -One or more tumors

T4 -Confluence of erythema covering equal or more than 80% body surface area

Node

N0 -No clinically abnormal lymph nodes; biopsy not required

N1a -Clinically abnormal lymph nodes; histopathology: dermatopathic lymphadenophaty, clone negative

N1b -Clinically abnormal lymph nodes; histopathology: dermatopathic lymphadenophaty, clone positive

N2a -Clinically abnormal lymph nodes; histopathology: early involvement of MF, clone negative

N2b -Clinically abnormal lymph nodes; histopathology: early involvement of MF, clone positive

N3 -Clinically abnormal lymph nodes; histopathology: partial or complete effacement of the lymph nodes; clone positive or negative

Nx -Clinically abnormal lymph nodes without histological confirmation or inability to fully characterize the histological subcategories

Visceral

M0 -No visceral organ involvement

M1 -Visceral involvement

Blood

B0a -Absence of significant blood involvement, clone negative

B0b -Absence of significant blood involvement, clone positive

B1a -Low blood tumor burden: more than 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2, clone negative

B1b -Low blood tumor burden: more than 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2, clone positive

B2 -High blood tumor burden: equal or less than 1,000/L Sézary cells with positive clone

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ISCL, International Society for Cutaneous Lymphoma; EORTC, European Organization for the Research and Treatment of Cancer, MF, mycosis fungoides.

1.6 Staging course (20)

All patients with MF should have a clinical examination, skin biopsies and an assessment of peripheral blood for atypical cells. Routine biochemical blood screening and chest X-ray should also be part of the procedure and enlarged lymph nodes should be biopsied. In patients with extra-cutaneous spread of the disease ultrasound of liver and spleen, isotope scans and computer tomography scans may be useful.

1.7 Treatment options in early stage MF (13,14, 21, 22, 23)

Early-stage MF including stage IA, IB and IIA have been treated with various agents, including topical corticosteroids, topical nitrogen mustard, topical carmustine, electron-beam radiotherapy, topical bexarotene, photochemotherapy, photodynamic therapy and oral retinoids.

1.7.1 Skin- Directed Therapy (SDT)

SDT includes topical steroids, topical chemotherapy, topical bexarotene, topical immunomodulator, radiotherapy and photochemotherapy. SDT shows a good approach in early-stage of MF. There is agreement that STD should be initially used in early-stage MF (21).

Topical corticosteroids

Topical corticosteroids are used in early-stage of MF with an overall response rate of >90% and they are usual good tolerated, but the side effects such as reversible skin atrophy or side effects typical for potent steroids such as decrease of cortisol level in serum, ecchymosis and light skin irritation may follow.

Topical chemotherapy

Nitrogen mustard (mechlorethamine hydrochloride, NM) and carmustine (BCNU) are also used in early-stage MF. Nitrogen mustard can be applied on the skin lesion as ointment or as aqueous base, which may have more sensitization effect. NM has a complete response rate of 79%-80% for IA stage and 35%-68% for stage IB. Application once or twice a day can be performed all over the body surface except face and genitals. Common side effect such as contact dermatitis can be reduced with ointment. In some patients other side effects are present including erythema, teleangiectasia and hyperpigmentation. There is some discussion about an increased non-melanoma skin cancer- risk due to NM, but most of the time NM was used in combination with other therapies, witch may support the risk.

Carmustine (BCNU) can be used topical as ointment or as aqueous base once per day in early-stage CTCL. BCNU side effect such as contact dermatitis is lower compared to NM, but this topical agent must be used with caution as it could cause leucopenia.

Topical retinoid

Bexarotene 1% gel is a synthetic retinoid, which shows a good therapy outcome in stage IA-IIA disease (overall response rate of 54% and a complete response rate of 10% patients). Topical application can be started once per day and further increased four times per day if the drug is well tolerated. Pregnant woman should not use this treatment. As topical agent, Bexarotene can induce a rash, irritation and erythema. Bexarotene is not sold in Europe, but can be achieved from the international pharmacy.

Topical immunomodulator

Imiquimod, a topical immunomodulator stimulates TH1 cytokines and induces apoptosis in basal cell carcinoma. There is also an effect for patches and plaques after using imiquimod 5% cream in MF.

Radiotherapy and electron-beam therapy

Superficial X-ray radiation, as low- dose 55 kV X-ray, may be used in the treatment of single tumor lesions. It is also practical to use conventional X-ray when PUVA treatment regimens or electron-beam is not available.

Electron-beam radiation can be used for the entire skin surface, as total skin electron-beam radiation (TSEB) or in limited lesions. Radiation with low energy electrons from linear accelerators penetrates less deep and toxic effects are only in the skin. The aim of TSEB is to reach skin clearing with fewer side effects. The usual dose applied on the whole skin can be from 20 to 30 Gy in a time period from 4 to 6 months. Some side effects such as temporary alopecia, nail fragility, telangiectasia, hands and feet edema, temporary anhidrosis and soreness of the skin may develop. Men could become infertile and female should have some contraception in the following 6 months after therapy. In patients with a higher stage and a tendency to relapse an additional therapy following electron-beam treatment should be considered because a long disease free-interval may be achieved.

Photochemotherapy

Psoralen plus long-wave ultraviolet A (PUVA) (24-33) or narrowband ultraviolet B (NB-UVB) (35-44) are effective treatments for patients with MF in early-stage disease.
PUVA was first reported in 1976 by Gilchrest et al. (24) and in 1977 by Roenigk (25). Psolaren is known to induce cell organelle damage in neoplastic T-cell populations by p53-independent programmed cell apoptosis as well as by protein-synthesis-independent mechanisms of pre-programmed cell death. PUVA is a widely used modality for the treatment of MF, but it has also been associated with various side effects and long-term risk of photocarcinogenesis (34). A long- term observation in a large cohort of psoriasis patients has been shown that there is a risk of squamous cell carcinoma associated with PUVA treatment (70).

Since 1999 narrow-band UVB (311nm) therapy (NB-UVB) was introduced to the treatment of MF. (36,38,39). The mechanism of NB-UVB, which induces neoplastic T-cell apoptosis in the skin, is not well defined. NB-UVB affects the antigen presentation ability of Langerhans cells by reducing their viability and function. Besides, it increases IL 2, IL 6 and TNF alpha production by human keratinocytes, which may affect immune-modulation and suppress the function of clonal neoplatic T-cell populations (45,46). Side effects from NB-UVB such as erythema or burning are easy to manage, but there are also reports of an association with the risk for skin cancer in mice studies (47). However, a retrospective study from Weischer et al. (48) found no evidence of an increased skin cancer risk in psoriasis patients treated with NB-UVB within a follow up period of 10 years. For early-stage MF patients it has been reported that NB-UVB treatment may have the same efficacy as PUVA treatment, but lower side effects (49).

Photodynamic therapy (PDT)

In PDT, topical photosensitizer, 5-aminolevulinic acid (5-ALA) is applied on the lesion and exposed to red light (630 nm). Malignant T-cells incorporate 5-ALA and become sensitive to light, which induces their apoptosis. An effect on single patches and plaques which had a bad response to other therapy regimens could be demonstrated. Side effects of 5-ALA could be pain that occurs during light exposure, erythema, edema and post-inflammatory pigment changes.

1.7.2 Biological- response modifiers

The role of the biological response modifiers is to target the malignant cells and to correct the immune dysfunction induced by malignant CD4+ cells proliferates. This targeted therapy regimens can be used for patients who have no response to other skin-directed treatments.

Interferon alpha (IFN-alpha)

INF-alpha is a TH1 cytokine with antitumor and immunomodulatory effects available as INF-alpha 2a and INF-alpha 2b. The dose and period of the treatment varies depending on patients' presentation, stage of the disease and tolerance to therapy. INF-alpha can be applied subcutaneously or directly onto the lesion. Well-tolerated is a start with low dosage and slow increase of the dose until clearing effect is reached. Side effects could be fever, fatigue, muscle pain and chill. Some patients may also develop depression, absence of appetite, and loose stools. Leucopenia, thrombocytopenia or thyroidal dysfunction can be present and demand regular blood monitoring.

Oral retinoid

Oral bexarotene is a synthetic retinoid, which binds selectively to the retinoid receptor and affects the regulation of cell proliferation, differentiation and cell death. The effective and safe dose is 300 mg/m2/daily. Most common side effects are hypertriglyceridemia, hypercholesterolemia and central hypothyroidism. There is also an increased risk of developing acute pancreatitis due to high triglyceride level, though additional therapy with some fibrats and statins are recommended. Regular monitoring of peripheral blood during therapy is obligate. Other side effects of bexarotene are increased liver parameters, headache, leucopenia and dry skin.

1.8 New treatment targets

The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the EORTC have developed consensus guidelines which are recommending a standardized general protocol design; a scoring system for assessing tumor burden in skin, lymph nodes, blood, and viscera; definition of response in skin, nodes, blood, and viscera; a composite global response score; and a definition of end points (23). However, these guidelines have not been prospectively or retrospectively validated for a large cohort of patients.

One review (14) presented an overview of recent molecular discoveries and targets for therapy in patients with MF. Some immune regulatory molecules such as IL-15, IL-16, and IL-21, and programmed death-1 (PD-1) were found to be overexpressed in CTCL, thus they may be targets for novel future therapies.

Th17-derived cytokines (IL-17, IL-21, and IL-22) was found to have a role as an IL-17-producing T-cell population in cutaneous lesions of patients with MF.
Chemokine receptor 4 (CCR4) is necessary for skin-homing of normal CD4+ T lymphocytes as well as for malignant CTCL cells and seems to be highly expressed in CTCL skin lesions. Anti-CCR4 is currently evaluated in clinical studies for patients with CTCL.
Cytotoxic T lymphocyte antigen (CTLA-4) inhibits T-cell activation and proliferation and confers resistance against activation induced cell apoptosis. Increased CTLA-4 expression was found in peripheral blood from patients with MF. Therefore, ipilimumab, an Anti-CTLA-4, may be a new potential therapeutic target in MF.

Some epigenetic mechanisms seem to down-regulate expression of tumor suppressor genes and lead to carcinogenesis. For example hypermethylation of CpG islands in promoter regions of genes leads to dysregulation of the cell cycle, apoptosis, DNA repair, chromosomal instability, and microsatellite instability genes and proteins. In early and advanced stages of mycosis promoter hypermethylation of p15, p16, and MLH was found and suggested to be responsible for acetylation of histones (a conformation of chromatin).

Histone deacetylases (HDACs) remove acetyl groups, regulate p53 tumor suppressor and E2F oncogene and are developed to restore tumor suppressor and cell regulatory genes.

However, the mechanisms of pathogenesis in CTCL have allowed the development of a bright spectrum of targeted therapies with a variety of combinations and more individualized treatments. Patients with early-stage MF have a very good prognosis and should be initially treated with skin-directed therapies.

1.9 Purpose

Psoralen plus long-wave ultraviolet A (PUVA) (24-33) or narrowband ultraviolet B (NB-UVB) (35-44) are commonly used therapy options for patients with early-stage MF. It has been recommended that treatment choice should depend on earlier treatment response of the patient, treatment availability and physician experience (49). After many years of experience in treatment of MF, it still remains undefined which type of phototherapy and which protocol might be optimal for patient with early-stage MF.

Previous studies have used some kind of maintenance therapy or combinations of therapies, which may have some influence on treatment outcome in terms of primary response and relapse-free interval. It is also difficult to define efficacy of the treatment modalities by themselves and to evalute which treatment should be used first.

The purpose of this cross-over study was not only to evaluate individual responses regarding treatment effect and relapse-free intervals after NB-UVB and PUVA therapy on the same patient without additional systemic therapy or maintenance treatment, but also to report side effects experienced with both therapy regimens in the same patient in early-stage MF.

2 MATERIALS AND METHODS

2.1 Patients characteristics

The present study was conducted from 2000 until 2009 at the Department of Photodermatology at the Medical University of Graz (Austria). Included were only patients with clinical and histologically proven early-stage MF (IA and IB stage). The stage of the disease was determined on the basis of type and extent of skin involvement according to the International Society for Cutaneous Lymphoma and the Cutaneous Lymphoma Task Force of the EORTC (30). Stage IA (T1, N0, M0, B0) refers to MF confined to the skin with limited patches, papules and/or plaques covering less than 10% of the skin surface (T1), with no clinically abnormal peripheral lymph nodes (N0), no visceral organ involvement (M0) and absence of significant blood involvement (B0). Stage IB refers to MF confined to the skin with equal to or more than 10% of limited patches, papules and/or plaques covering the skin surface (T2, N0, M0, B0). The following data were obtained in this study: patients' characteristics (gender, age, skin phototype, pretreatment disease stage and pretreatment disease duration; Table 3) NB- UVB and PUVA treatment regimen (number of treatments, treatment duration and radiation dose), primary response, relapse-free interval and side effects after both treatments.

Table 3.Clinical characteristics of patients with early-stage mycosis fungoides

		Nr. of patients (n = 18)
Gender, n (%)	female	6 (33)
	male	12 (67)
Phototype, n (%)	I	2 (11)
	II	10 (56)
	III	6 (33)
Stage, n (%)	IA	3 (17)
	IB	15 (83)
Mean age, years (range)		64 (43-83)
Mean disease duration, months (range)		62 (2-300)

2.2. Therapy regimen

Patients were randomized to receive either NB-UVB therapy or PUVA therapy.
NB-UVB was given using a Waldmann 7001 box; (Waldmann Medizinische Technik, Gevelsberg Germany) equipped with 40 100-W fluorescent lamps (TL-01; Philips Company, Eindhoven, the Netherlands). The treatment was 3 times a week and initial treatment dose was 70% of the predetermined minimal erythema dose.
PUVA therapy was applied 3 times weekly using a Waldmann PUVA 7001 K box (Waldmann Medizintechnik, Villingen-Schwenningen, Germany) equipped with Waldmann F85 ⁄ 100 W-PUVA fluorescent bulbs. Eight-methoxypsoralen (Oxsoralen; Gerot Pharmazeutika GmbH, Vienna, Austria, 0.6 mg/kg body weight to the nearest 10 mg) was given one hour prior to UVA exposure. The initial UVA dose was 50%–70% of the minimal phototoxic dose (mean 1.1 J⁄cm^2) and was increased weekly by 20%-40% of the previous dosage in patients with no erythema after therapy.

Patients without erythema after NB-UVB or PUVA treatment achieved a 20% increase of the previous dose once a week. In patients who showed slight erythema after treatment, the previous dose was repeated. If patients achieved moderate erythema the next dose was reduced whereas in patients who achieved severe erythema, the treatment was paused and continued with the last well tolerated dose.

Each treatment was continued until at least 95% clearing of the patient's skin lesions had occurred. In the follow-up interval the patients were controlled in the second, fourth, twelfth, eighteenth and twenty fourth months. Relapse was defined as clinically diagnosed patch-stage MF requiring further therapy. Those patients, who relapsed after the first treatment regimen, received the other treatment regimen in the second treatment period. The relapse-free interval (months) was recorded in follow-up period 1 after the first treatment regimens and in the follow-up period 2 after the second treatment regimens.

2.3 Statistical analysis

The sample size calculation was done according to table 9.2 from Machin et al. (50). Thirty three patients would be sufficient assuming a two-sided log rank test with relapse proportion 0.5 in one group and 0.1 in the other group at some time after end of treatment in order to achieve 90% power at alpha equal 0.05. The trial design was changed into a two period cross-over study as it turned out that relapse rate was higher than assumed. Relapse rates were estimated by the Kaplan-Meier method. Relapse free times were compared between treatments through an extended proportional hazards model (62). In this model a baseline hazard rate was assumed for each follow-up period. The model measured the treatment effect through the logarithm of the ratio of hazard rates. This log hazard ratio was assumed to be zero under the null hypothesis. 95% confidence intervals (CI) were calculated from the standard error of the logarithm of the hazard ratio. A robust estimator of the standard error accounted for the additional dependence due to same patients being treated in both periods. The squared ratio between the naïve and the robust estimator of the standard error measures how many more treatments would have been needed if the study design had been parallel groups instead of crossover. $P < 0.05$ was considered statistically significant. R 2.13.1 (www.r-project.org) was used for analysis.

3 RESULTS

3.1 Patient outcome

Eighteen patients were randomized to the first treatment regimen with NB-UVB or PUVA. Ten patients received and completed NB-UVB treatment and eight patients had PUVA treatment as first treatment regimen (Table 4). More then 95% clearing of MF skin lesions could be achieved in all our patients (n=18) after the first treatment regimen with NB-UVB (Fig.2) and PUVA (Fig. 3), respectively. Four patients completed only NB-UVB therapy and two patients completed only PUVA therapy as first treatment regimen, because they did not relapse during follow-up period 1 (NB-UVB: n=3, PUVA: n=1) or died in the follow-up interval without having relapsed (NB-UVB: n=1, PUVA: n=1). Twelve patients relapsed after the first treatment regimen and received a second treatment regimen (NB-UVB: n=6; PUVA: n=6). All patients finished the second treatment period and achieved clearing of more than 95% of MF lesions.

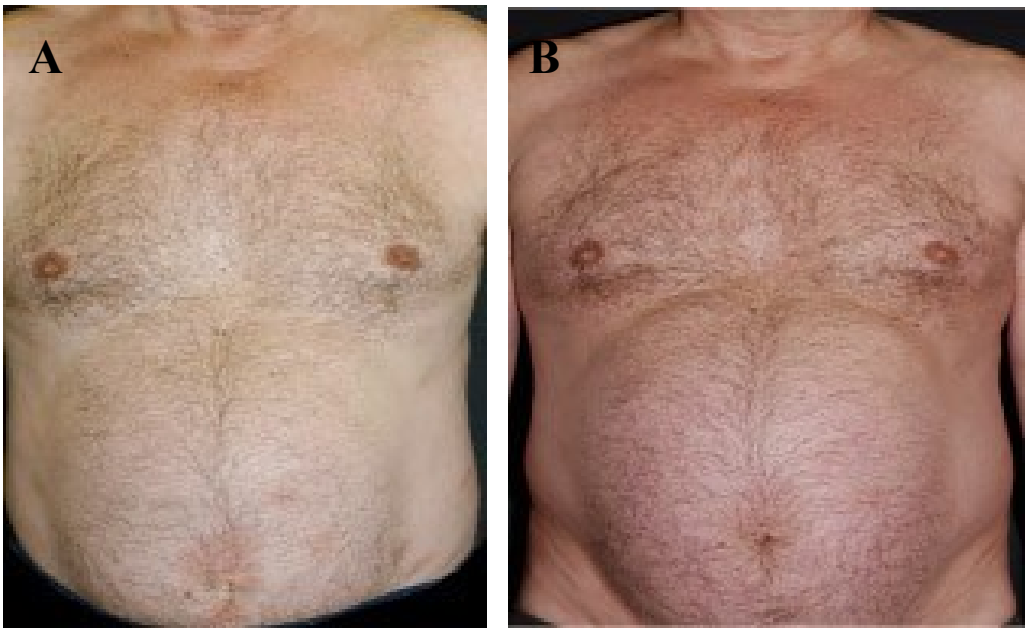

Fig. 2. Clinical presentation of a 70-year-old man with MF before NB-UVB **(A)** and after NB-UVB **(B). The total number of** treatments was 25.

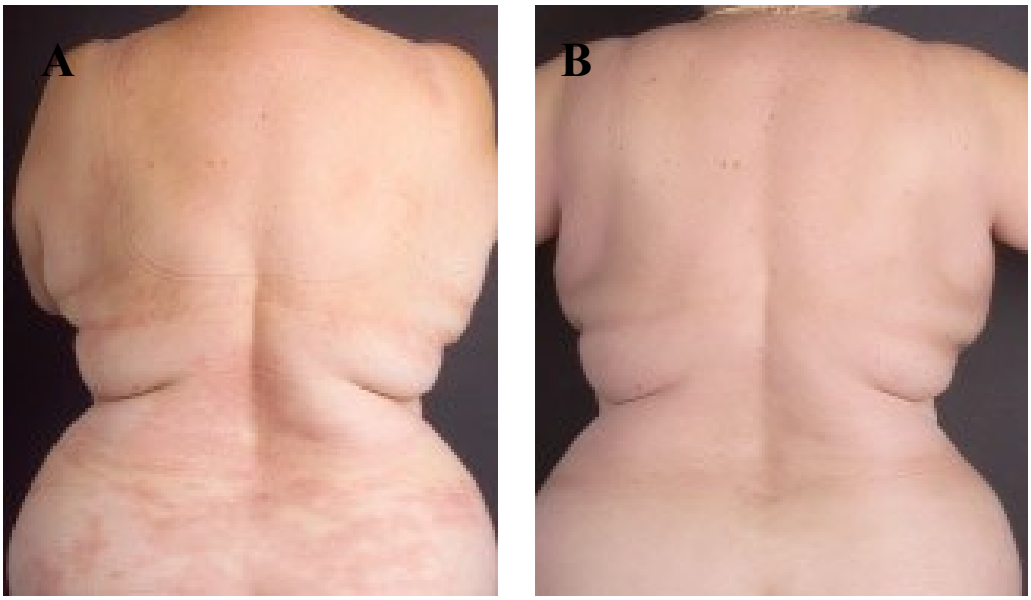

Fig. 3. Clinical presentation of a 61-year-old woman with MF before PUVA **(A)** and after PUVA **(B). The total number of** treatments was 29**.**

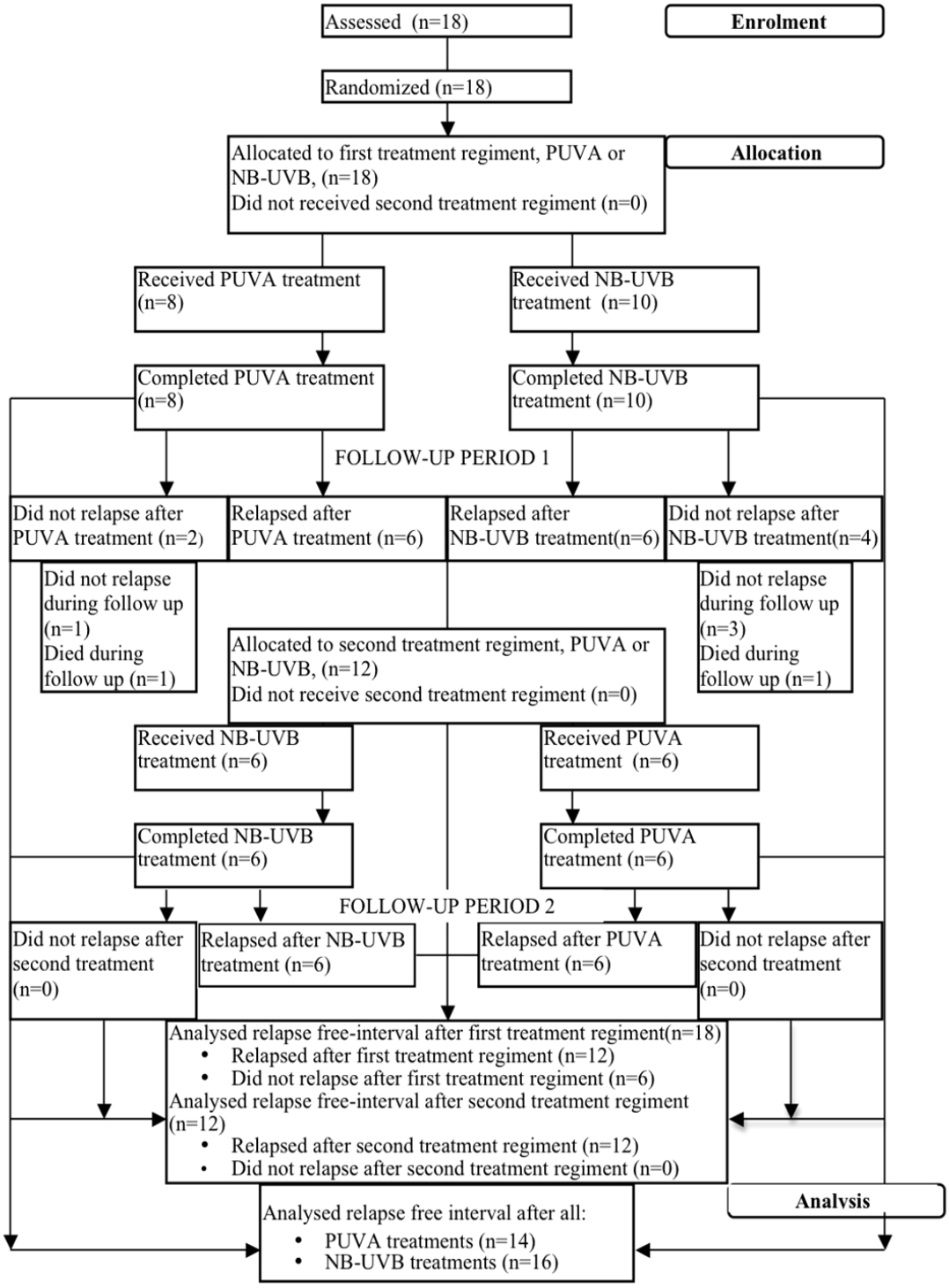

Fig. 4 Patients' flow chart

3.2. Therapy comparison

Overall, 16 NB-UVB treatments and 14 PUVA treatments were completed and analysed in a total of 18 patients. Twelve patients had both treatments (cross-over patients) and 6 had single treatment (NB-UVB: n=4; PUVA: n=2). All patients achieved complete clearing. A comparison between the two treatment regimens did not show a significant difference according to the number of treatments nor the treatment duration. Further detailed results are shown in Table 5.

Table 5. Comparison of phototherapy treatments

	NB-UVB (n = 16)	PUVA (n = 14)	*p*-Value*
Mean number of treatments	27.8 ± 6.6	26.2 ± 8.2	0.576
Mean treatment duration (months)	2.4 ± 0.7	2.5 ± 0.9	0.667
Mean relapse-free interval (months)	21.3 ± 22.9	20.5 ± 19.8	0.922

*ANOVA

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

Kaplan-Meier analysis of all treatments showed no difference between the two treatment modalities in terms of relapse-free interval (Fig. 5).

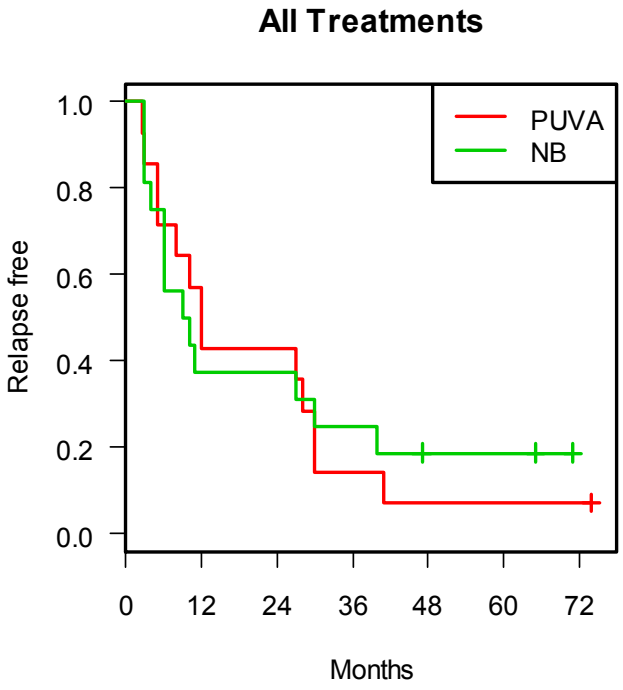

Fig. 5. Kaplan–Meier analysis of relapse-free interval after narrowband ultraviolet B treatment (NB-UVB; n = 16) and psoralen plus ultraviolet A treatment (PUVA; n = 14). There was no significant difference in the time between the two treatments (p = 0,89).

A relapse of MF skin lesions was observed in 12 out of 16 (75%) patients treated with NB-UVB and in 12 out of 14 (86%) patient treated with PUVA in the follow-up period 1 after the first treatment and follow-up period 2 after the second treatment, respectively. Median time to relapse was 12 months in follow-up period 1 and 8 months in follow-up period 2. Kaplan-Meier estimates of relapse rates for each follow-up period are shown in Fig. 5.

The hazard ratio of relapse between NB-UVB and PUVA was 0.86 (95% CI: 0.43 to 1.7). The treatment differences were not statistically significant (p=0.66). The squared ratio of standard errors was 1.6, which indicated that the power of the cross-over trial with 18

patients was equivalent to parallel group trials with 28 patients.

There was a significant follow-up period effect (p=0.019). The hazard ratio between the follow-up period 1 and the follow-up period 2 was 2.07 (95% CI: 1.13-3.8).

The screening for additional risk factors for relapse (age, gender, duration of disease, phototype and stage) only identified disease stage as significant (p=0.001. The hazard ratio between stage IA and stage IB was 6.9 (95% CI: 2.64-18).

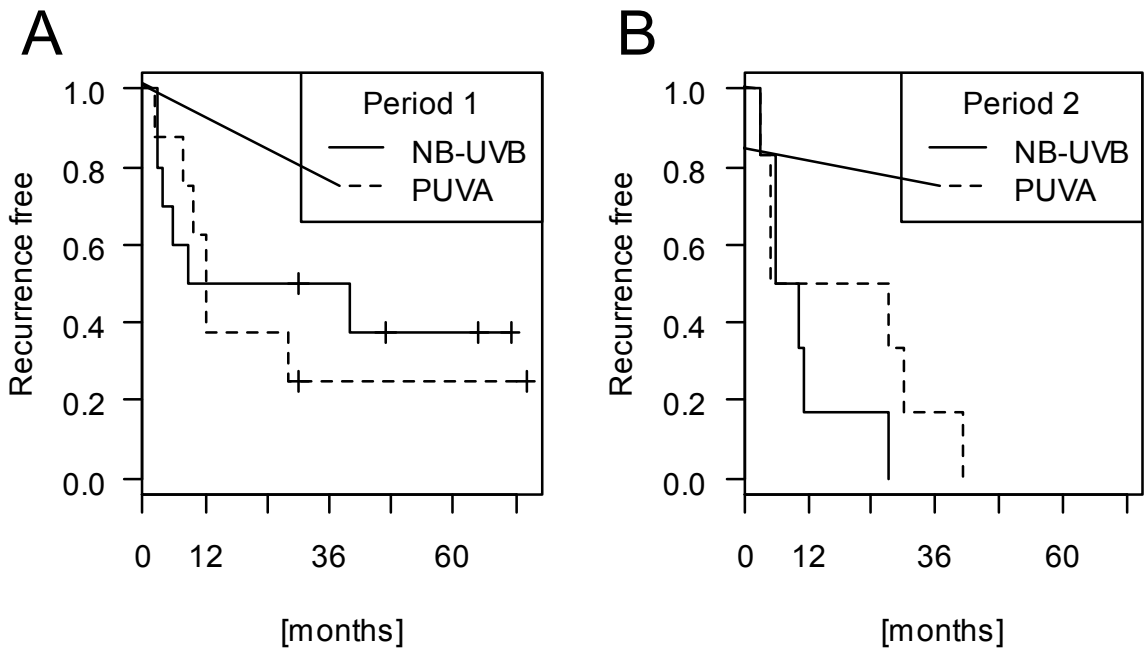

Fig. 6. Kaplan–Meier analysis of relapse-free intervals of patients with mycosis fungoides after psoralen plus ultraviolet A treatment (PUVA; n = 14) and narrowband ultraviolet B (NB-UVB; n = 16) in follow-up period 1 (A) and follow-up period 2 (B). There was no significant difference in relapse-free interval between NB-UVB and PUVA therapy (p=0.66).

3.3. Side effects

Five out of 16 (31%) patients with NB-UVB treatment and ten out of 14 (71%) patients with PUVA treatment had side effects. Side-effects were detected to be statistically significant different between the two treatment groups (Chi-square=4.821; p = 0.028), however, the difference was mainly due to gastrointestinal side effects during PUVA therapy, which can not be expected during NB-UVB treatment. One patient complained about side effects during both treatments (burning after NB-UVB and an easily controlled polymorphic light eruption after PUVA therapy). All other patients had side effects with either of the treatment regimens. A total of 4 patients treated with PUVA reported burning sensations or generalized erythema. Four patients had gastrointestinal complaints after systemic psoralen intake and 2 patients had an easily controlled polymorphic light eruption. During NB-UVB therapy 5 patients achieved mild erythema. (Table 6)

Table 6. Side effects after phototherapy with NB-UVB and PUVA for patients with patch-stage mycosis fungoides

	Number of side effects with	
	NB-UVB	PUVA
Burning/erythema	5	4
Gastro-intestinal tract	0	4
Polymorphic light eruption	0	2

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

4 DISSCUSION

In previous studies NB-UVB was reported to be equivalent or almost equivalent in terms of response, effectiveness and safety compared to the established PUVA therapy regiment for MF treatment (31,51,52). NB-UVB was recommended for patients with patch- and plaque- stage MF, as it was found to be an effective and well-accepted treatment. The incidence of some acute side effects such as erythema varied between 10% and 94% according to therapy regiment, to the definition of erythema and acute side effect such as polymorphic light eruption, are rare and can be seen with NB-UVB therapy as well as with PUVA treatment. However, the long-term risk of skin cancer remains recognized, but not exactly quantified and it should be discussed with the patient (53).

Our NB-UVB and PUVA results are similar to other published reports though many of them were retrospective studies with larger number of patients, using different concomitant and maintenance therapy.

Table 6. Comparison of the efficacy NB-UVB and PUVA treatment for mycosis fungoides

NB-UVB	Total (n)	CR (n)	RFI	PUVA	Total (n)	CR (n)	RFI
Hofer et al. (36))	6	5	6	Akaraphanth et al. (32)	8	7 §	25.5
Clark et al. (38)	8	6	20	Honigsmann et al.(27)	44	44	22
Gathers et al. (39)	24	13	12.5	Rosenbaum et al. (29)	43	43	6.3
Ghodisi et al. (40)	16	12	4.5	Querfeld et al (30).	104	66	39 *
Pavlovsky et al. (41)	68	55	NR	Ahmad et al (31).	28	18	10 *
Brazzelli et al (42)	20	18	8	Powell et al (28).	19	8	NR
Our results for NB-UVB	16	16	21.3	Our results for PUVA	14	14	20.5

NB-UVB, narrow band ultraviolet B; PUVA, psoralen plus ultraviolet A; n, number of patients: CR, complete response; RFI, mean relapse free interval (months); NR, not recorded; * median; § Two patients with unknown time of relapse.

Phototherapy treatment regimen and value of maintenance therapy

Over 30 years PUVA was the treatment of first choice for patients with MF. A recently published literature review by Carter et al. (54) showed that the complete clinical response rate for PUVA was ranging from 58% to 88% for 2 to 3 times per week, 42% to 86% for 3 times per week and 64% to 86% for 2 to 4 times per week. They concluded that initial treatment regimen using PUVA 2 to 3 times per week, should continue until clearance. After clearance of skin lesion, 88% of the responders achieved some kind of maintenance therapy with treatment frequency ranging from once per week to once per month. However, the evidence of maintenance therapy benefit is difficult to find because many of the studies had different study designs, limited numbers of MF patient in different disease stages, diverse combination therapies or a lack of standardized maintenance therapy regimens.

Another study (30) reported that patients were treated with PUVA in early-stage MF, 2 to 3 times per week, until complete clinical remission was achieved (66 of total 104 patients), and performed maintenance therapy from once a week to once every six weeks for 61 patients of 66 patients. Thirty-one patients with maintenance therapy had a relapse and another 30 patients with maintenance therapy remained in remission. Three of a total of 5 patients who had no maintenance therapy had relapsed. Half of the 66 patients had a complete clinical remission for 84 months (range, 5 to 238 months) and 33 patients relapsed after median disease-free interval of 39 months (range, 2 to 127 months). The effect of maintenance therapy on the disease-free interval still remains unclear.

In a prospective cohort study, Sánchez et al. (55) analyzed the data of patients with maintenance therapy with PUVA during follow-up of 28 months. They found that maintenance therapy with PUVA does not prevent a future relapse and found that the history of relapse is strongly associated with future relapse (relative risk = 10.38, 95% confidence interval 2.64-40.72).

Wackernagel et al. (56) who evaluated the relapse-free intervals of patients with or without PUVA maintenance therapy also could not find significant differences.

Since 1999 NB-UVB has been reported to be effective in a number of studies and case reports with early-stage MF patients. Complete clinical response could be achieved in 54% to 91% of MF patients in stage IA to IIA treated with NB-UVB 3 times per week. In

the survey group 59% of responders used maintenance therapy with different frequencies from once per week to once per month during an interval of more than 5 years. In these studies there are pro and contra arguments using maintenance therapy but the question of the value of maintenance therapy concerning relapse prevention and relapse-free interval prolongation still remains undefined (54).

Pavlotsky et al (41) treated 67 patients with NB-UVB therapy and 43 patients with broad band UVB (BB-UVB) therapy and achieved complete clinical remission in 86% of patients with stage IA and 71% of patients with stage IB in both groups. For all patients who achieved complete clinical remission maintenance therapy was performed. The group found no differences in terms of non-relapse rate between patients with or without maintenance therapy. They concluded that treatment should be stopped after complete clinical remission was achieved and recommended maintenance therapy only in patients who had relapsed after first cleaning regimen.

Boztepe et al. (44) achieved complete clinical remission in 11 out of 14 patients with early-stage MF treated with NB-UVB after a mean of 25 treatments. Eight patients completed maintenance therapy with a median duration of 18 months and a mean number of 112.6 treatment sessions. The maintenance protocol was 3 times per week for 3 to 6 months, twice per week for 3 to 6 months, once per week for 3 to 6 months, once biweekly for 3 to 6 months and once monthly for 3 to 6 months without increasing the previous UVB dose. Mean relapse-free interval was 26 months. They concluded that maintenance therapy may prolong the relapse-free interval. However, in comparison to our results after a mean number of 27.8 treatments without maintenance therapy, the relapse free rates were only a little bit longer.

Ponte et al. (52) recommended to start the maintenance therapy once the response reached a plateau or with the aim to achieve a longer relapse-free interval. They advised to give maintenance PUVA treatments at the beginning twice weekly for 8 weeks and they reduced to once weekly for another 4 to 8 weeks. For NB-UVB maintenance treatments they advised to start twice weekly for 4 to 8 weeks and reduce to once weekly for another 4 to 8 weeks. With this protocol they could achieve CR in 12 (68.4%) of 19 patients with NB-UVB therapy and 59 (62.1%) of 95 patients with PUVA therapy, respectively. The mean relapse-free interval was 14.0 months in the NB-UVB group and 11.5 months in the PUVA group. In our study without maintenance treatment after NB-UVB or PUVA treatment; however we achieved a mean relapse-free interval of 20.5 months for NB-UVB patients and 21.3 months for PUVA patients.

As these results were similar to those with maintenance treatment, we concluded that patients with complete response and long remission times after the last treatment do not need maintenance treatment with NB-UVB or PUVA.

Treatment response in correlation to stage of the disease

Hermann et al. (33) used data from five studies to calculate the rate of complete remission after PUVA therapy and found that 90% of patients in stage IA, 76% in stage IB, 78% in stage IIA, 59% in stage IIB and 61% in stage III had complete clinical response.

Powell et al. (19) concluded that response to PUVA therapy depends on the stage of the disease. Complete clinical remission was achieved by 7 of 10 patients with early-stage disease and 3 patients had more than 80% of skin clearance. Patients with higher stages of MF did not respond well to PUVA therapy according to their results.

Hönigsmann et al. (27) reported in a study with 44 MF patients treated with PUVA that 5 of 9 patients in stage IA and 10 of 26 in stage IIB had no relapse in a follow up period of 79 months. All patients with higher stages (T3) relapsed in the observation period. The mean relapse-free interval was 20 months for patients in stage IA and 17 months for patients in stage IIB.

In a single centre retrospective cohort analysis by Querfeld et al. (30), 66 of a total of 104 MF patients with clinical stages IA to IIA achieved complete clinical remission after PUVA therapy. Relapse free-interval rates at 5 and 10 years of follow-up for all patients in stage IA were found to be 56% and 30 %, respectively; and 74% and 50% for stage IB and IIA, respectively. No statistical difference between the non-relapsed and the relapsed group regarding actuarial survival rates at 5, 10 and 15 years was detected (94%, 82% and 82% for patients with stage IA, respectively and 80%, 69% and 58% for patients with stages IB and IIA, respectively). They concluded that long-term survival is not affected by the relapse status.

Hofer et al. (36) treated 20 patients (6 patient with early stage MF and 14 patients with small plaque parapsoriasis) with NB-UVB and found that 19 patients (5 of 6 patients with early stage MF and 14 of 14 patients with small plaque parapsoriasis) had a complete clinical remission after 3 to 4 treatments per week for 5 to 10 weeks.

Brazzelli et al. (42) treated 20 patients with 50% patients in stage IA and other 50% patents in stage IB until more than 95% clearance of the patient skin lesions was achieved. 90% of the patients achieved complete clinical remission after a mean of 29 treatments. The patients relapsed in a mean period of 8 months.

Another study with 24 patients treated with NB-UVB, 12 of them in stage IA and 12 in stage IB of MF, reported that 13 (54% IA, IB) patients had complete clinical remission, 7 (29% IA, IB) patients had partial clinical remission and 4 (17% IA, IB) patients had no response. In repeated biopsies 9 of 10 patients with complete clinical remission showed histological clearing. After treatment stop, 4 patients with complete clearance had a relapse with a mean time to relapse of 3 months (39).

Gökedemir et al. (43) found a correlation between complete clinical remission and histological remission except for patients in the plaque stage. In this study 18 patients had patch stage and 5 patients had plaque-stage of MF according to histopathological examination. All patients in the patch group had a complete response, whereas from the plaque group 3 (60%) patients had CR, 2 (40%) had partial response (PR) or no response (NR). Histological results showed that 17 (94.4%) patients had complete clearing and 1 (5.6%) patient had a partial improvement in the patch group. Histological complete clearing was found in 1 (20%) patient and partial or no improvement in 4 (80%) patients from the plaque group.

Ahmad et al. (31) demonstrated that the majority of the patients (79%) with stage IA and IB of MF (60% of these in the NB-UVB group and 62% in the PUVA group) had a complete response. Patients with IIA stage disease needed more treatment exposure to achieve complete response in both therapy groups compared to patients with stage IA and IB.

Similar results have been found by Diederen et al. (51), who described no differences between complete response rates (81% vs. 71%) and relapse-free intervals (24.5 vs. 22.8 months) in this retrospective study with stage IA and IB patients after NB-UVB vs. PUVA therapy, respectively.

In our study we included MF patients with stage IA und IB, but not with IIA. All our patients achieved a clearing of at least 95% of the former skin lesions. We decided not to take complete clearance as endpoint because in Caucasians single lesions may remain as

postlesionel hyperpigmented patches even, if the treatment duration was increased.

Value of the combination systemic therapies with phototherapy

Some of the previous comparative studies combined systemic therapies such as retinoids, corticosteroids and methotrexate with UV treatment.

The most common therapy combinations with PUVA are interferon-alpha (INF-alpha) and bexarotene. One study reported the combination therapy of INF-alpha 2a (dosage from 6 to 30 million units 3 times a week) and PUVA in 15 CTCL patients. Complete clinical response was achieved in 80% and partial response in 13% of the patients. As INF-alpha 2a may have a photosensitizing effect with phototoxic reaction lower UVA dose were recommended for the combination therapy with PUVA (57).

Mostow et al. (58) reported 5 patients in stage IA and IB, who were resistant to PUVA therapy but achieved complete clearance after an average of 3.2 months INF-alpha therapy (6 million units daily) combined with PUVA twice weekly.

Combination of PUVA therapy with the retinoid bexarotene has been reported as effective and safe treatment regiment (59).

El-Mofty et al. (60) assessed in a right- left comparative study in early stage MF patients whether the addition of psoralen with a NB-UVB therapy could be beneficial compared to NB-UVB or PUVA as mono-therapy. However, they found no significant difference between the treatment regimens.

The intent of a combination therapy is to lower the cumulative dose and number of treatments, to achieve higher remission rates and to prolong relapse-free intervals. In general, the question whether there is a benefit in a combination therapy with PUVA compared to PUVA mono-therapy seem to remain unsolved. However, a combination regimen could be considered in cases of insufficient response or rapid relapse after PUVA therapy.

Side effects and risk of photocarcinogenesis

Our patients treated with light therapy had more PUVA associated side-effects than UVB associated side-effects.

PUVA associated side-effects included nausea, vomiting, headache after psoralen intake, increasing risk of phototoxicty, higher ocular lens photosensitivity for UVA, induction of photocarcinogenesis and photoimmunosupression (61).

After each PUVA treatment session the use of UV-protective lenses is demanded and avoidance of sun exposure is stricter than after NB-UVB treatment. On the other side, NB-UVB treatment might be more practical for patients because they don't have to swallow a medication and systemic side-effects do not occur.

Acute side-effects of NB-UVB are erythema, burning, blistering, xerosis, pruritus, immunosupression and the appearance of a polymorphic light eruption (53). However, in most cases such side-effects do not force the interruption of UV-therapy. NB-UVB treatment can even be used in comorbid patients, children or pregnant women (63). Benign pigmentary disorders such as lentigines are often observed after long- term PUVA therapy, but very uncommon, after NB-UVB therapy (64).

Some studies have reported about an increased risk of developing non-melanoma skin cancer and melanoma in patients with psoriasis after long-term PUVA treatment (65,66,70).

Stern (65) found after 30 years follow-up that psoriasis patients with more than 350 PUVA treatments had a greatly increased risk of squamous cell carcinoma (SCC) and after 150 PUVA treatments there was a modest effect on SCC risk. However, the basal cell carcinoma (BCC) risk was not greatly increased even after high dose PUVA exposure.

Stern also reported in PUVA follow-up studies that after 15 years of first PUVA exposure an increased risk of melanoma could be observed. Especially patient, who had high cumulative doses of PUVA had a greater risk to develop melanoma (66). The evidence of long-term PUVA safety in psoriasis patients in terms of an increased photocarcinogenesis risk associated with treatment dose should be considered in patient informed consent.

Similar large long-term follow-up PUVA studies are not available for patients with MF, but some literature point out that there may be similar risks to develop non-melanoma

skin cancer (67).

The risk of photocarcinogenesis after NB-UVB was suspected to be lower than after PUVA therapy (68). The reason may be a lower cumulative UVB dose in treatment protocols containing minimal radiation in the more mutagenic 290-310 nm range (45).

In one report (69) 1908 patients treated with NB-UVB had follow-up for a median period of 4 years (range, 0.04-13). No significant increase of squamous cell carcinoma or malignant melanoma could be found in this study. A small increase of basal cell carcinoma has been found, but several of the tumors were discovered in the first 3 months and may be not related to treatment. More retrospective studies with longer follow-up periods are needed to determinate the true carcinogenic risk of NB-UVB treatment (53,69).

Summary and Limitation of the study

According to our data we were able to demonstrate that NB-UVB achieved similar results as PUVA regarding response rates and relapse-free intervals. The deeper radiation penetration of PUVA was assumed to lead to better clinical responses and to a longer relapse-free interval, however our prospective report confirms that NB-UVB can be as effective as PUVA in treatment in early-stage MF.

A principal limitation of the present study was the small number of patients participating in the treatment of early-stage MF. Furthermore, the results were obtained in a heterogenic group of MF patients. Despite limitations, the major strength of the study was the presentation of the outcome results, which are clinically relevant to treat early-stage MF.

Some reports recommend maintenance therapy with aim to achieve prolonged relapse-free interval. However, more retrospective studies are necessary to evaluate the effect of maintenance therapy according to the relapse free-interval.

As MF is a slow progressing disease and patients requiring repeated radiations may profit from combinations therapies and lower cumulative UV-doses, but more retrospective reports are needed to report which combination therapies achieve best outcome.

NB-UVB should be considered as a first therapy option for patient with early-stage MF (IA and IB) and recurrent episodes of the disease. The patients with disease progression or insufficient NB-UVB therapy response should be switched to PUVA therapy (21).

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5 FIGURE LEGENDS

5.1 Figure list

5.2 Table list

6 RESUME

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Prospective randomized cross-over comparison study of narrowband UVB (311nm) and PUVA therapy in the treatment of patch-stage mycosis fungoides

A. Sugic, F. Legat, A. Gruber-Wackernagel, F. Quehenberger, P. Wolf, A. Hofer