Potential of narrow-band ultraviolet B to induce sustained durable complete remission off-therapy in patients with stage I mycosis fungoides

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Background: Narrow-band ultraviolet B (NB-UVB) is a first-line therapy for stage I mycosis fungoides (MF), with a complete response in 75%-85% of patients. However, data on long-term disease-free survival (DFS) after therapy are scarce.

Objective: To assess the long-term DFS after NB-UVB treatment of stage I MF.

Methods: We used a historic cohort of all stage I MF patients achieving a complete response with NB-UVB who discontinued treatment before 2011. Age at the beginning of phototherapy, sex, stage, skin phototype, number of treatments, total dose, and the length of DFS was collected.

Results: Of the 117 patients who started NB-UVB, 93 patients (80%) had a complete response and 56 (60%) were disease free as of March 2017. In a multivariate analysis, DFS was affected independently by age and disease stage only. DFS was longer for patients <50 years old (124 months) than those ≥50 years old (91 months, P = .01) and longer for stage IA patients (131 months) than stage IB patients (87.6 months, P = .001).

Limitations: The study was retrospective in nature.

Conclusion: After a single course of NB-UVB, over a half of stage I MF patients achieved >5 years of DFS and were potentially cured. Thus, NB-UVB can be considered a disease-modifying therapy. (J Am Acad Dermatol 2019;80:1550-5.)

Key words: complete response; disease-free survival; mycosis fungoides; narrow-band UVB.

Several options for treatment of stage I mycosis fungoides (MF) exist, and complete response (CR) is achieved in up to 90% of patients.[1,2] Among these treatments, narrow-band ultraviolet B (NB-UVB) is to date the treatment of choice of most institutions.[1,3] In our previous study of stage I MF patients treated by NB-UVB, 84% of stage IA and 78% of stage IB patients achieved CR. Among the patients who achieved CR, 65% had not relapsed after an average follow-up of 27 weeks from complete cessation of phototherapy.[1] Despite the high CR rate, it is generally accepted that there is no cure for

Abbreviations used:

CR:	complete response
DFS:	disease-free survival
MF:	mycosis fungoides
NB-UVB:	narrow-band ultraviolet B
PUVA:	psoralen ultraviolet A

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MF with the available therapeutic modalities. Therefore, disease control and alleviating patients' symptoms are the sole goals of treatment.[2] However, on the basis of a 2.5-year follow-up study, it was suggested that total skin electron-beam radiation is potentially curative even for stage IB patients.[4] Recently, curative potential was suggested for phototherapy (NB-UVB and bath psoralen ultraviolet A [PUVA]) with just a 1-year follow-up.[5] The purpose of our study was to examine the long-term disease-free survival (DFS) rate at ≥5 years in stage I MF patients after CR induction with NB-UVB.

CAPSULE SUMMARY

- Narrow-band ultraviolet B (NB-UVB) produces high rates of complete response for patients with stage I mycosis fungoides. Data on long-term remission off therapy are lacking.
- NB-UVB induced >5 years disease- and therapy-free survival in ~60% of complete response patients.
- NB-UVB can be considered a disease-modifying and potentially curative therapy for patients with stage I mycosis fungoides.

METHODS

Study population and methods

This study was approved by the local ethics committee. This study was a retrospective analysis of patients with stage I MF treated with NB-UVB therapy at the Phototherapy Unit of the Department of Dermatology, Sheba Medical Center (Tel Hashomer, Israel). To ensure ≥5 years of DFS data, patients were included only if they started their first NB-UVB course during 2003-2010, achieved CR and then stopped all therapy (including NB-UVB maintenance and topical steroids) by the end of 2011 or earlier, and had a follow-up period of ≥5 years. For all patients, stage I MF was defined by using the International Society of Cutaneous Lymphoma and European Organisation for Research and Treatment of Cancer criteria.[6] The treatments given in a UV 1000 L booth (Herbert Waldmann GmbH & Co KG, Schwenningen, Germany), and the irradiances were checked routinely with a UVB detector (Herbert Waldmann GmbH & Co KG) with an average of 11.2 mW/cm^2.

The treatment algorithm is presented in Fig 1. It is our policy to set the starting doses according to the skin type (0.05 J/cm^2 for skin types 1-2 and 0.1 J/cm^2 for skin types 3-5). All patients were initially treated thrice weekly on nonconsecutive days (genital areas shielded). NB-UVB dose was increased each treatment according to skin type (0.05 J/cm^2 for skin types 1-2 and 0.1 J/cm^2 for skin types 3-5) for a maximum dose of 3 J/cm^2. We defined CR as 100% clinical disappearance of all lesions, as recently suggested by the United States Cutaneous Lymphoma Consortium.[3]

All patients achieving CR were recommended maintenance treatment. The dose that was required to achieve CR was used throughout maintenance therapy, and frequency of treatments was decreased. Thus, maintenance was given twice a week for about 4 weeks, then once a week for about the 4 weeks, and finally every 2 weeks—except in rare cases of extremely photosensitive skin that could only tolerate a maximum intertreatment interval of 7-10 days. Maintenance was discontinued after 3-6 months. Patients followed up at our outpatient clinic at least every 6 months. At every visit, the patients were questioned and examined for a disease recurrence, even a minor one. Specifically, they were asked if they used topical steroids or had intentional sun exposure purposely for disease control. Disease recurrence was defined as an obvious clinical finding or was biopsy proven for doubtful cases. For all patients, their age at the start of phototherapy, sex, stage (IA or IB), skin phototype according to Fitzpatrick classification, number of treatments, total phototherapy dose, and length of DFS was collected.

Statistical analysis

Statistical analyses were performed by using the SPSS24.0 version software. The differences in DFS duration regarding categorical variables (ie, sex, age, disease stage, skin phototype, number of treatments, and total phototherapy dose) were analyzed by using Kaplan Meier survival analysis and log rank test. Cox multivariate regression analysis was used to assess the relationship between these variables and DFS duration.

RESULTS

In total, 117 stage I MF patients started NB-UVB during 2003-2010. Of these, 93 patients (80%) had a CR and 56 (60%) had no recurrence as of March 2017. None of these patients passed away. There were 22 clinically clear-cut recurrences; another 15 doubtful cases were proven by biopsy.

The characteristics of the 93 patients with CR and the 56 patients without relapse after ≥5 years are shown in Table I. In a univariate analysis (Fig 2), the DFS was 124 months and 91 months for patients <50 years and ≥50 years, respectively (P = .01).

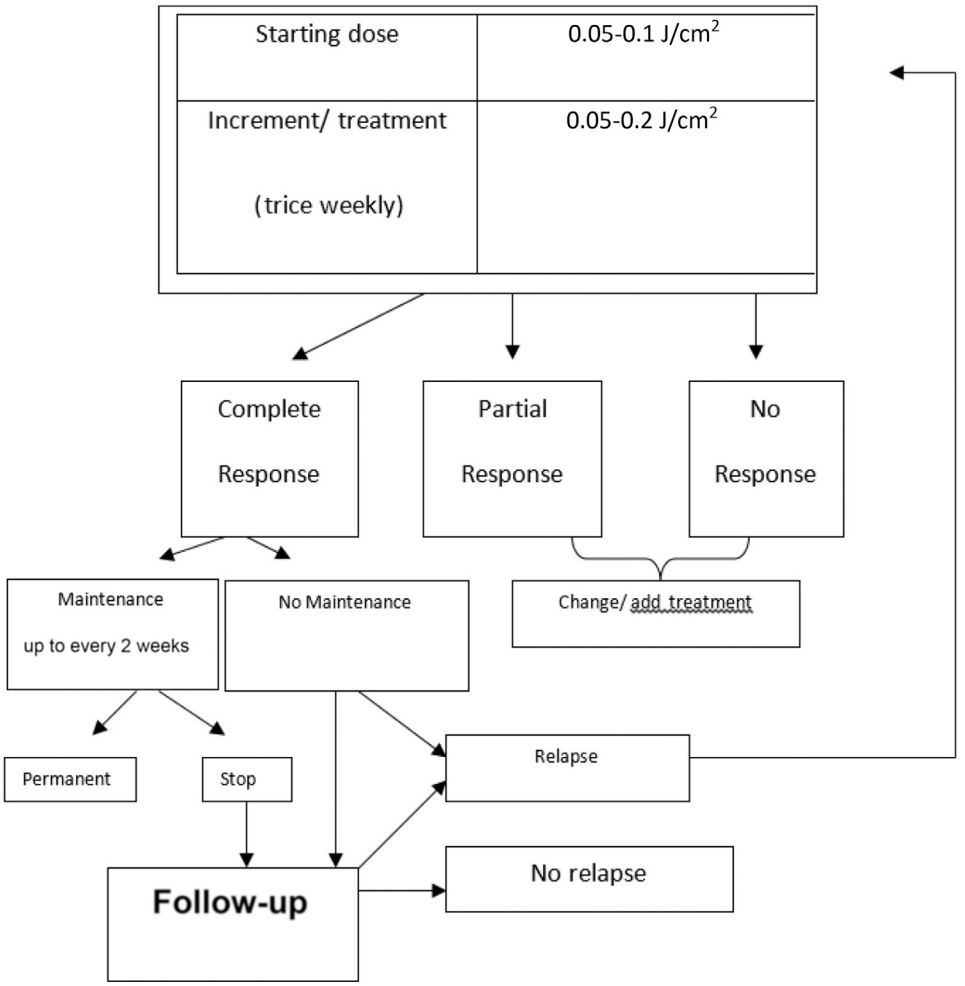

Fig 1. Narrow-band ultraviolet B treatment algorithm for stage I mycosis fungoides.

Similarly, the DFS was 131 months and 87.6 months for stage IA patients and stage IB patients, respectively (P = .001). The DFS for patients given a total cumulative NB-UVB dose of <40 J/cm^2 was 123 months compared with 91 months for patients given a higher cumulative dose (P = .015). Improved survival was also observed for those with a reduced number of treatments; the DFS for patients with <50 treatments was 118 months compared with 93 months for patients with a higher number of treatments (P = .097). Both sex and skin phototype had no effect on the recurrence rate.

In a multivariate analysis (Fig 3), the DFS was significantly shorter for stage IB patients aged ≥50 years (72 months) than for the other 3 patient groups stratified by stage and age (106-142 months).

DISCUSSION

The long path to a possible cancer cure for MF starts with a CR, defined as a tumor burden of zero.[7] With therapy, the survival of patients with stage IA disease can be expected to be the same as age- and sex-matched controls.[8,9] Nevertheless, it is generally accepted that there is currently no cure for MF.[2] Yet earlier studies showed that a curative response, defined as a disease-free period greater than either 5 or 8 years after therapy completion, can be achieved.[10,11] Because the term cure in cancer, in general[12] and particularly in MF, is vague and might require a tumor-specific definition, it is currently better to discuss sustained complete remission after therapy. There are several, skin-targeted treatment options for stage I MF.[1,13] Among these, NB-UVB is the current treatment of choice in most institutions. In the current study, a CR was achieved in 80% of stage I MF patients. These results are comparable to what has been previously reported regarding skin-targeted treatments in MF in general and NB-UVB in particular.[1] Yet data on the DFS period after CR is limited, and when available, the follow-up periods are relatively short. Furthermore, in many of these reports, the patients were still on maintenance

Table I. Characteristics of stage I MF patients achieving complete response after NB-UVB therapy and those with a complete response at last follow-up visit ≥5 years later

	Last treatment	Last follow-up visit	
Characteristic	**N**	**n (%)**	***P* value**
Sex			
Male	62	37 (60)	.976
Female	31	19 (61)	
Age, years			
<50	46	34 (74)	.010*
≥50	47	22 (47)	
Skin type			
1-2	34	20 (59)	.4
3-5	59	36 (61)	
Stage			
1A	42	33 (79)	.001*
1B	51	23 (45)	
Total UVB dose, J/cm^2			
<40	47	34 (73)	.015*
≥40	46	22 (48)	
Treatments, n			
<50	51	34 (67)	.097
≥50	42	22 (53)	
Total	93	56 (60)	

MF, Mycosis fungoides; *NB-UVB,* narrow-band ultraviolet B.
*Log rank test (Mantel-Cox).

therapy, thus not enabling the drawing of conclusions on the disease-modifying effect of the therapy or sustained complete remission without maintenance therapy.

The CR rate with topical mechlorethamine is 50-90% with DFS of 5 years in up to one third of stage 1 MF patients.[11,14-16] However, many of these patients had continued maintenance therapy. PUVA studies showed a CR of 79%-90% in stage IA patients and 59%-76% in stage IB patients, with up to a 47% and 75% relapse rate, respectively, especially when off maintenance therapy.[1] In the latest PUVA study of a small group of patients with patches and limited plaques, all showed a CR. Half of them retained the CR after 3-18 years of follow-up.[17] High-dose UVA-1 therapy induced a CR in 7 of 8 patients with stage IB disease; however, long-term follow-up was not reported.[18] Total skin electron-beam radiation leads to a CR in 60%-95% of patients. Most relapses occur within the first year after the end of therapy and rarely after 3 years, especially for the group with limited plaques.[4,19] Similarly, long-term DFS was achieved for unilesional MF treated with targeted radiation therapy.[12]

A CR can be achieved with various forms of artificial UVB (broad band and narrow band) in 63%-83% of stage I MF patients, as summarized and further shown in our previous study.[1] In total, 49% of patients with a CR after NB-UVB therapy did not relapse while completely off treatment, after an average follow-up of 77 weeks.[1] Elcin et al[20] reported on CR (defined as >95% clearing) in 30 of 33 stage I MF patients treated with NB-UVB; 70% of these patients stayed relapse free for 20-119 months (median ~2.5 years). However, all but 1 patient had maintenance therapy during the disease-free period.

In a recent study, Almohideb et al[5] retrospectively analyzed a cohort of 267 stage I patients treated initially with either bath PUVA (158 patients) or NB-UVB (109 patients). Overall, 88% of patients in both groups achieved CR. The median DFS was 43 months for bath PUVA and 15 months for NB-UVB. Although not clarified in the text, it seemed that patients were on maintenance therapy while free of disease.

In the current study of 117 stage I MF patients treated with NB-UVB, 80% had CR and 60% were disease-free for ≥5 years without any maintenance therapy. This represents a substantial number of stage I MF patients disease free without use of therapy for a long enough period to be considered in analogy to solid tumors as potentially cured. Thus, NB-UVB might be a disease-modifying therapy in early stage MF.

Nevertheless, 40% of our initially CR patients relapsed. Thus, our second goal of the study was to identify the predictive factors for disease relapse. Several previous studies have investigated prognostic factors besides clinical stage. Elevated lactate dehydrogenase, advanced age, male sex, peripheral eosinophilia, large cell transformation and folliculotropic MF were all associated with poor prognosis.[21-27] Using retrospective data from 29 international sites, the Cutaneous Lymphoma International Consortium identified 4 factors (stage 4, age >60 years, large cell transformation, and increased lactate dehydrogenase) to be independently associated with worse survival.[27] One should bear in mind that those studies included patients in all stages of the disease.

In a univariate analysis of our retrospective cohort, older age (≥50 years old), stage IB and higher cumulative dose of NB-UVB or more NB-UVB sessions were identified as risk factors for relapse and associated with shorter DFS. In a multivariate analysis, only age and disease substage prevailed. Stage IA was a protective factor for disease relapse, as expected and as was previously reported by Almohideb et al.[5] Younger age was also an independent protective factor in our study. This observation is in accordance with the risk factors described previously[21-27] but contradictive of the findings of Almohideb et al,[5] who found older age to be a

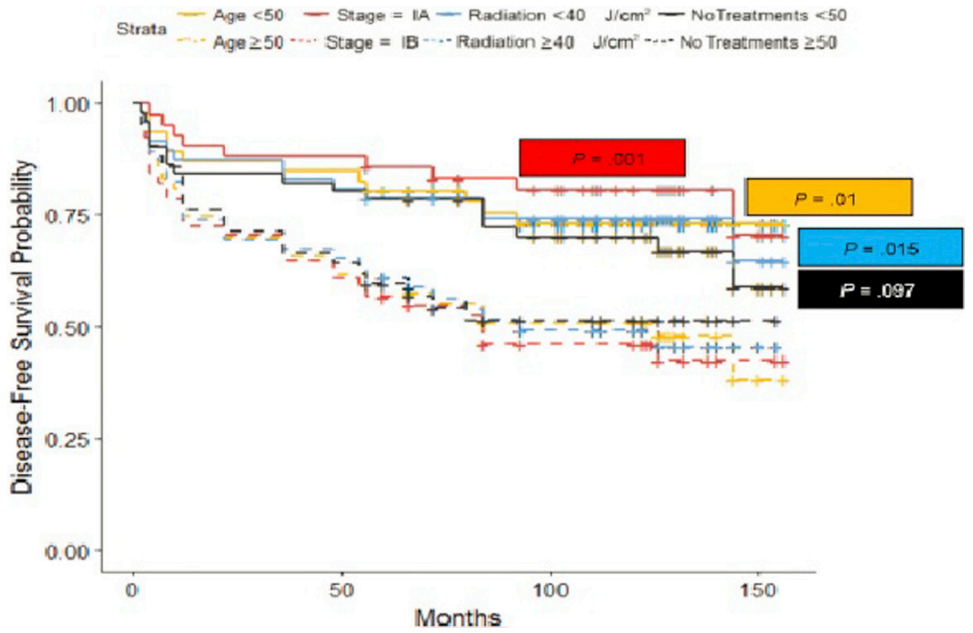

Fig 2. Disease-free survival by age, stage, total narrow-band ultraviolet B dose, number of treatments, sex, and skin phototype.

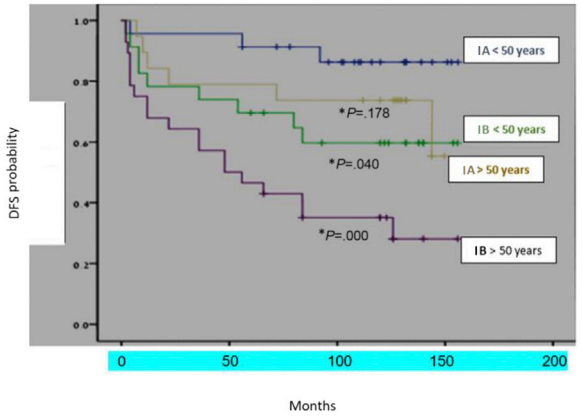

Fig 3. Disease-free survival multivariate analysis by stage and age. *P value relative to stage IA, <50-year group. *DFS*, Disease-free survival.

protective factor. Whether age has a different effect on disease course in early MF, or this finding is a mere coincidence remains to be studied. Both sex and skin phototype had no effect on the recurrence rate.

One cannot ignore that the limitations of our study are mainly due to its retrospective nature. When evaluating patient stage, we could not assess whether patients had only patches, only plaques, or both. Therefore, although all patients were in complete remission after NB-UVB therapy, we could not stratify by exact initial tumor burden. It is possible that the differences in DFS between the cumulative doses and number of treatments reflect lesion morphology. Yet in the multivariate analysis, therapy intensity was a dependent factor for DFS. In addition, despite the fact that all patients were asked at follow-up about relapses, use of topical steroids, and intentional tanning, occasional events might not have been remembered. We also could not stratify for the degree of natural tanning as part of a patients' life style. Nevertheless, even if these factors had been confounders, their effect should be minimal.

In summary, our study suggests that NB-UVB is a disease-modifying treatment of stage I MF that results in a large proportion of patients with DFS >5 years; therefore, this treatment has a curative potential. Younger patients of stage IA have a better chance of achieving this outcome.

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